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(71) Applicant: **Regeneron Pharmaceuticals, Inc.**
Tarrytown, NY 10591 (US)

(72) Inventors:
- **CROLL, Susan, D.**
  Putnam, NY 10579 (US)
- **MACDONALD, Lynn**
  White Plains, NY 10605 (US)
- **MURPHY, Andrew, J.**
  Croton-on-Hudson, NY 10520 (US)

(74) Representative: **J A Kemp**
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

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(54) **HUMAN ANTIBODIES TO GFR 3 AND METHODS OF USE THEREOF**

(57) The present disclosure provides antibodies that bind to human GFRα3 and methods of using same. According to certain embodiments, the antibodies are fully human antibodies that bind to human GFRα3. The antibodies described herein are useful for the treatment of diseases and disorders associated with one or more GFRα3 biological activities, including the treatment of acute or chronic pain conditions, or inflammatory conditions.

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Description

FIELD OF THE INVENTION

[0001] The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind to human glial cell-line derived neurotrophic factor (GDNF) family receptor alpha 3 (GFRα3), and therapeutic methods of using those antibodies.

STATEMENT OF RELATED ART

[0002] The glial cell line-derived neurotrophic factor related family is composed of glial cell line-derived neurotrophic factor (GDNF), neurturin (NRTN), artemin (ARTN) and persephin (PSPN). Each member of the GDNF family binds to a glycosylphosphatidylinositol (GPI)-anchored receptor associated with the plasma membrane. This family of receptors is referred to as the GDNF-family receptor alphas (GFRαs). This receptor family is composed of four different GFRα receptors, GFRα1-4. GDNF binds preferentially to GFRα1, NRTN binds preferentially to GFRα2, ARTN binds preferentially to GFRα3, and PSPN binds preferentially to GFRα4. Each GDNF family ligand signals through the RET ("rearranged during transfection") receptor tyrosine kinase, which was first discovered as a proto-oncogene. RET is activated by GDNF family members only if the ligand is first bound to its GFRα receptor (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394).

[0003] Both ARTN and GFRα3 are highly expressed during development and are involved in sympathetic nervous system development. In adult, GFRα3 expression is largely restricted to the sensory neurons of the dorsal root ganglia (DRG) (Orozco, O.E., et al., European J. Neuroscience, (2001), 13:2177-2182). In adult mouse, artemin is expressed in testis, uterus, thyroid, prostate, and epididymis, as well as in olfactory bulbs and arterioles in the intestine and mesentery (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394; Airaksinen, M.S. et al., Brain, Behavior and Evolution, (2006), 68:181-190).

[0004] A possible role for GFRα3 and artemin in hyperalgesia has been shown in several studies. For example, it has been demonstrated that an injection of the artemin protein into the hindpaw of a rodent caused thermal hyperalgesia and this nociception was enhanced when artemin was co-injected with NGF (Malin, S.A., et al., J. Neuroscience, (2006), 26(33): 8588-8599). Other studies showed that artemin mRNA expression was upregulated in a murine inflammatory model (Elitt, C.M., et al., J. Neuroscience, (2006), 26(33): 8578-8587). Furthermore, other studies showed that artemin transgenic mice have elevated expression of TRPV1 and TRPA1 and have increased behavioral sensitivity to heat and cold (Elitt, C.M., et al., J. Neuroscience, (2006), 26(33): 8578-8587). In addition, a possible role for GFRα3 in visceral hypersensitivity has been shown by studies in GFRα3 knockout mice, whereby these mice showed attenuation of visceral hypersensitivity after intracolonic treatment with TNBS

[0005] (2,4,6-trinitrobenzene sulfonic acid) relative to wild type C57BL/6 mice (Tanaka, T., et al., Am. J. Physiol. Gastrointest. Liver Physiol. (2011), 300:G418-G424). A possible role for artemin and its receptor GFRα3 in pain associated with pancreatitis has also been shown by a study done in patients undergoing pancreatic head resection (Ceyhan, G.O., et al., Gut, (2007), 56:534-544). Based on the foregoing, further studies are warranted to determine whether patients suffering from pain/hyperalgesia and/or hypersensitivity could benefit by treatment with an inhibitor of GFRα3 activity.

[0006] Antibodies that bind GFRα3 are described in US 6,861,509. In addition, US 6,677,135 discloses a full length GFRα3 sequence, whereas splice variants of the GFRα3 molecule are described in US 7,026,138; US2007/0232535 and US2006/0216289. US 7,138,251 discloses sequences that have 99% identity to full length GFRα3 and the preparation of humanized monoclonal antibodies to this molecule is described in this patent.

BRIEF SUMMARY OF THE INVENTION

[0007] In a first aspect, the invention provides fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that bind to human GFRα3 and inhibit or block its activity, for example, block the binding of GFRα3 to the glial cell line-derived neurotrophic factor, artemin, and possibly blocking the subsequent activation of the RET receptor tyrosine kinase and/or blocking signaling through RET and/or blocking signaling through a mediator other than RET. The antibodies or antigen binding fragments thereof may be useful for treating hyperalgesia, allodynia and/or hypersensitivity to any sensory stimulus, including, but not limited to pressure, heat and/or cold. The antibodies may also be used to treat pain/hypersensitivity associated with a wide range of conditions and disorders in which blocking the interaction of GFRα3 with artemin is desired. The antibodies may also be used to inhibit tumor cell growth, proliferation and/or metastasis.

[0008] In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to human GFRα3 and has one or more of the following characteristics:

(i) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance;
(ii) demonstrates the ability to block about 50-100% of the binding of GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM;
(iii) demonstrates the ability to block about 20% to about 100% of the binding of GFRα3 to a solid support coated with a mixture of artemin and RET;
(iv) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM;
(v) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain;
(vi) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo;*
(vii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis;
(viii) does not cross-react with other GFR co-receptors for RET;
(ix) comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; or
(x) comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0009] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof is selected from the group consisting of a murine, chimeric, humanized and a human antibody.

[0010] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof does not cross-react with human GFRα1 or human GFRα2.

[0011] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises (a) a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397 and (b) a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0012] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof demonstrates the ability to block about 50-95% of the binding of human GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 750 pM.

[0013] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof blocks about 75-100% of the binding of human GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 400 pM to about 15 nM.

[0014] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of human RET with an IC_{50} ranging from about 300 pM to about 5 nM.

[0015] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of cynomolgus RET with an IC_{50} ranging from about 0.7 nM to about 2.5 nM.

[0016] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194,210, 226,242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0017] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397.

[0018] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0019] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 381/389 and 397/405.

[0020] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NO: 50/58, 146/154, 210/218 and 290/298.

[0021] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 383 and 399;
(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 385 and 401;
(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 387 and 403;
(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 391 and 407;
(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 393 and 409; and
(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 395 and 411.

[0022] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof competes for specific binding to human GFRα3 with an antibody or antigen-binding fragment comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362, 381/389 and 397/405.

[0023] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof binds the same epitope on human GFRα3 that is recognized by an antibody comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362, 381/389 and 397/405.

[0024] The antibodies of the invention can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933).

[0025] In one embodiment, the isolated antibody or antigen-binding fragment thereof that binds specifically to human GFRα3, comprises a HCVR comprising the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within the HCVR amino acid sequences selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; and/or a LCVR comprising the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the LCVR amino acid sequences selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See, e.g.,* Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani et al., J. Mol. Biol. 273:927-948 (1997); and Martin et al., Proc. Natl. Acad. Sci. USA 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0026] In one embodiment, the isolated antibody or antigen-binding fragment that specifically binds human GFRα3 comprises:

(a) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 387 and 403; and
(b) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 395 and 411.

[0027] In one embodiment, the isolated antibody or antigen-binding fragment that specifically binds human GFRα3, as described in (a) and (b) above, further comprises:

(c) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 383 and 399;
(d) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 385 and 401;
(e) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 391 and 407; and

(f) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 393 and 409.

[0028] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human GFRα3, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210,226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 387 and 403, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 395 and 411 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 383 and 399 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 385 and 401 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 391 and 407 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 393 and 409 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance; (vi) demonstrates the ability to block about 50-100% of the binding of GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM; (vii) demonstrates the ability to block about 20% to about 100% of the binding of GFRα3 to a solid support coated with a mixture of artemin and RET; (viii) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM; (ix) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain; (x) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo*; (xi) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis; (xii) does not cross-react with other GFR co-receptors for RET.

[0029] In one embodiment, the present invention provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain having an amino acid sequence selected from any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0030] In one embodiment, the invention provides an antibody or fragment thereof further comprising a HCDR1 domain having an amino acid sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence of any of those shown on Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0031] In certain embodiments, the antibody or antigen-binding portion of an antibody that specifically binds to human GFRα3 comprises a HCDR3/LCDR3 amino acid sequence pair selected from any of the HCDR3/LCDR3 amino acid sequences shown in Table 1. According to certain embodiments, the antibody or antigen-binding portion of an antibody comprises a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOs: 8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/112, 120/128, 136/144, 152/160, 168/176, 184/192, 200/208, 216/224, 232/240, 248/256, 264/272, 280/288, 296/304, 312/320, 328/336, 344/352, 360/368, 387/395 and 403/411.

[0032] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 4, 6 and 8, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 12, 14 and 16, respectively.

[0033] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and

HCDR3 sequences of SEQ ID NOs: 20, 22 and 24, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 28, 30 and 32, respectively.

[0034] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 36, 38 and 40, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 44, 46 and 48, respectively.

[0035] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 52, 54 and 56, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 60, 62 and 64, respectively.

[0036] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 68, 70 and 72, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 76, 78 and 80, respectively.

[0037] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 84, 86 and 88, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 92, 94 and 96, respectively.

[0038] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 100, 102 and 104, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 108, 110 and 112, respectively.

[0039] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 116, 118 and 120, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 124, 126 and 128, respectively.

[0040] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 132, 134 and 136, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 140, 142 and 144, respectively.

[0041] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 148, 150 and 152, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 156, 158 and 160, respectively.

[0042] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 164, 166 and 168, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 172, 174 and 176, respectively.

[0043] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 180, 182 and 184, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 188, 190 and 192, respectively.

[0044] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 196, 198 and 200, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 204, 206 and 208, respectively.

[0045] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 212, 214 and 216, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 220, 222 and 224, respectively.

[0046] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 228, 230 and 232, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 236, 238 and 240, respectively.

[0047] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 244, 246 and 248, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 252, 254 and 256, respectively.

[0048] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 260, 262 and 264, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 268, 270 and 272, respectively.

[0049] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 276, 278 and 280, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 284, 286 and 288, respectively.

[0050] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 292, 294 and 296, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 300, 302 and 304, respectively.

[0051] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 308, 310 and 312, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 316, 318 and 320, respectively.

[0052] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 324, 326 and 328, respectively and LCDR1, LCDR2 and LCDR3 sequences of

SEQ ID NOs: 332, 334 and 336, respectively.

[0053] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 340, 342 and 344, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 348, 350 and 352, respectively.

[0054] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 356, 358 and 360, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 364, 366 and 368, respectively.

[0055] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 383, 385 and 387, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 391, 393 and 395, respectively.

[0056] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 399, 401 and 403, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 407, 409 and 411, respectively.

[0057] Certain non-limiting, exemplary antibodies and antigen-binding fragments of the invention comprise HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 domains, respectively, selected from any of the amino acid sequences shown in Table 1.

[0058] In a second aspect, the invention provides nucleic acid molecules encoding anti-GFRα3 antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0059] In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 380 and 396 or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 49, 145, 209 and 289.

[0060] In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, 388 and 404 or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 57, 153, 217 and 297.

[0061] In one embodiment, the invention also provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence located within the variable regions from any of the antibodies shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain encoded by a nucleotide sequence selected from any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0062] In one embodiment, the invention provides an antibody or fragment thereof further comprising a HCDR1 domain encoded by a nucleotide sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain encoded by a nucleotide sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain encoded by a nucleotide sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain encoded by a nucleotide sequence shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0063] In a third aspect, the invention features a human anti-hGFRα3 antibody or antigen-binding fragment of an antibody comprising a HCVR encoded by nucleotide sequence segments derived from V_H, D_H and J_H germline sequences, and a LCVR encoded by nucleotide sequence segments derived from V_K and J_K germline sequences, with combinations as shown in Table 2.

[0064] The invention encompasses anti-hGFRα3 antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0065] In a fourth aspect, the invention features a pharmaceutical composition comprising a recombinant human antibody or fragment thereof, which specifically binds hGFRα3 and a pharmaceutically acceptable carrier. In one embodiment, the invention features a composition, which is a combination of an antibody or antigen-binding fragment of an antibody of the invention, and a second therapeutic agent. The second therapeutic agent may be any agent that is advantageously combined with the antibody or fragment thereof of the invention, for example, an agent capable of reducing pain, such as, but not limited to, opioids, morphine, a COX-2 inhibitor, aspirin, or other non-steroidal anti-

inflammatories, acetaminophen, duloxetine, local anesthetics, NMDA modulators, cannabinoid receptor agonists, P2X family modulators, VR1 antagonists, and substance P antagonists. The second therapeutic agent may be an interleukin-1 (IL-1) inhibitor, for example, a fusion protein (US 6,927,044); or an antiepileptic/anticonvulsant drug, such as gabapentin, pregabalin, topiramate; or a tricyclic antidepressant, such as amitriptyline; a cytokine inhibitor or antagonist, such as an antagonist to IL-6, IL-6R, IL-18 or IL-18R, or an inhibitor of a voltage-gated sodium channel, such as a $Na_v1.7$ inhibitor, or a $Na_v1.8$ inhibitor, or a $Na_v1.9$ inhibitor; an inhibitor of a potassium channel or calcium channel; or a NGF inhibitor (a small molecule inhibitor or an anti-NGF antibody), or a second inhibitor or antagonist to GFRα3, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of GFRα1, GFRα2 or GFRα4, an inhibitor of an acid sensing ion channel (e.g. ASIC1 or ASIC3), or a selective serotonin reuptake inhibitor (SSRI), or a serotonin norepinephrine reuptake inhibitor (SNRI), or an inhibitor of a prekineticin receptor (e.g. PROK1 and PROK2), or a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig, or a corticosteroid. The second therapeutic agent may be a small molecule drug or a protein/polypeptide inhibitor. The second therapeutic agent may be synthetic or naturally derived. The second therapeutic agent may be a second antibody specific for GFRα3, a polypeptide antagonist, a siRNA or an antisense molecule specific for GFRα3. It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

[0066] In a fifth aspect, the invention features methods for inhibiting hGFRα3 activity using an anti-hGFRα3 antibody or antigen-binding portion of an antibody of the invention, wherein the methods comprise administering a therapeutically effective amount of one or more antibodies of the invention, or antigen binding fragments thereof, or a pharmaceutical composition comprising one or more antibodies of the invention or antigen-binding fragments thereof.

[0067] In a sixth aspect, the invention features a method for treating a GFRα3-related condition or disease, or the pain associated with a GFRα3-related condition or disease, the method comprising administering an anti-GFRα3 antibody or antigen-binding portion of an antibody of the invention, or a composition comprising an anti-GFRα3 antibody or a fragment thereof, to a patient in need thereof, wherein the GFRα3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

[0068] In one embodiment, the invention provides for the isolated antibody or antigen-binding fragment thereof, or a pharmaceutical composition comprising at least one antibody or antigen-binding fragment thereof of the invention for use in treating a GFRα3-related condition or disease, or the pain associated with the GFRα3-related condition or disease, wherein the GFRα3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

[0069] In one embodiment, the invention provides for use of an isolated antibody or antigen-binding fragment thereof of the invention, or a pharmaceutical composition comprising at least one antibody of the invention in the manufacture of a medicament for treating a GFRα3-related condition or disease, or the pain associated with the GFRα3-related condition or disease, wherein the GFRα3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

[0070] In one embodiment, the GFRα3-related condition or disease is selected from the group consisting of acute pain, chronic pain, neuropathic pain, inflammatory pain, a functional pain syndrome, arthritis, pancreatitis, osteoarthritis, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, neurodegenerative disorders, movement disorders, neuroendocrine disorders, ataxia, visceral pain, acute gout, post-herpetic neuralgia, diabetic neuropathy, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, post-surgical pain, hereditary erythromelalgia, dental pain, rhinitis, cancer pain, complex regional pain syndrome (CRPS), inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and bladder disorders.

[0071] In one embodiment, the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome.

[0072] In one embodiment, the cancer pain is associated with a cancer selected from the group consisting of endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, non-small cell lung cancer, brain cancer, a leukemia, a lymphoma, bone cancer and pain associated with metastasis of a cancer.

[0073] In one embodiment, the antibody or antigen-binding fragment is administered to the patient in combination with a second therapeutic agent.

[0074] In one embodiment, the second therapeutic agent is selected from the group consisting of an opioid, a COX-2 inhibitor, a local anesthetic, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a second GFRα3 antagonist, a cytokine or cytokine receptor antagonist, a nerve growth factor (NGF) inhibitor (a small molecular inhibitor or an anti-NGF antibody), aspirin, a NSAID, a steroid, morphine, a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a tricyclic, an inhibitor of a voltage-gated sodium channel (Na_v), a calcium channel inhibitor, a potassium channel inhibitor, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of an acid sensing ion channel (ASIC1 or ASIC3), an anticonvulsant (gabapentin or pregabalin), an inhibitor of a prekineticin receptor (PROK1 and PROK2), a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig and a corticosteroid.

[0075] In one embodiment, the second GFRα3 antagonist is a small organic molecule, a second antibody specific for GFRα3, a polypeptide antagonist, a siRNA or an antisense molecule specific for GFRα3.

[0076] In one embodiment, the cytokine or cytokine receptor antagonist is an interleukin-1 (IL-1) antagonist, an IL-6 antagonist, or an IL-18 antagonist.

[0077] The disorder treated is any disease or condition, which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of hGFRα3 activity. Specific populations treatable by the therapeutic methods of the invention include a disease, disorder, or condition selected from acute, chronic, ischemic, neuropathic, or inflammatory pain, hypersensitivity, such as visceral, thermal, or mechanical hypersensitivity, chronic pancreatitis, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epileptic conditions, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, inflammatory bowel disease, spleen inflammation, stomach pain, trigonitis, fibroids, peritonitis, faecal urgency, incontinence, rectal hypersensitivity, visceral pain, osteoarthritis pain, post-herpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, breakthrough pain, post-surgical pain, cancer pain, or chemotherapy-induced pain. Other conditions treatable by the therapeutic methods of the invention include Hirschsprung disease, hereditary erythromelalgia, bladder disorders, rhinitis, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, a hematologic (blood-borne) cancer, such as a leukemia or a lymphoma, bone cancer, or pain associated with metastasis of a cancer, for example, pain associated with metastasis of a cancer to the bone. The antibodies of the invention or antigen-binding fragments thereof may also be used to treat the following conditions: non-malignant acute, chronic, or fracture bone pain; rheumatoid arthritis, spinal stenosis; neuropathic low back pain; myofascial pain syndrome; pancreatic; chronic headache pain; tension headache; diabetic neuropathy; HIV-associated neuropathy; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome (CRPS, also known as Reflex Sympathetic Dystrophy); phantom pain; intractable pain; acute musculoskeletal pain; joint pain; acute gout pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; burn and trauma pain; endometriosis; herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis pain; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; Fabry's disease pain; bladder and urogenital disease; and hyperactivity bladder. In one embodiment the antibodies of the invention may be used to treat a functional pain syndrome, wherein the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome.

[0078] The antibodies of the invention or antigen-binding fragments thereof may also be used to inhibit tumor cell growth/proliferation, or metastasis of tumor cells. In certain embodiments, the antibodies of the invention or antigen-binding fragments thereof, may be used to treat a cancer, or the "pain associated with a cancer" or "cancer-associated pain", including, for example, but not limited to, endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, a hematologic (blood-borne) cancer, such as a leukemia or a

lymphoma, bone cancer, or pain associated with metastasis of a cancer, for example, pain associated with metastasis of a cancer to the bone. "Cancer-associated pain" also includes pain more generally associated with cancerous conditions such as, e.g., renal cell carcinoma, pancreatic carcinoma, head and neck cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, malignant mesothelioma, multiple myeloma, synovial sarcoma, thyroid cancer, or melanoma. The antibodies of the present invention are also useful for treating or preventing pain caused by or associated with cancer therapy or anti-cancer medical treatments, e.g., chemotherapy-induced neuropathic pain such as pain caused by or associated with treatment with paclitaxel (Taxol™), docetaxel (Taxotere®); nitrosourea, cyclophosphamide, doxorubicin, epirubicin, 5-fluorouracil, topotecan, irinotecan, carmustine, estramustine, and platinum-based chemotherapeutic compounds, such as cisplatin, carboplatin, and iproplatin.

[0079] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0080]

Figure 1. Inhibition of artemin-sensitized capsaicin thermal hyperalgesia in animals injected with mouse GFRα3 antibodies (indirect blocker M1M6977N or direct blocker M1M6986N, n=8 each) or isotype (negative) control antibody (M2M180N, n=8) at 30mg/kg s.c. 2 days before receiving capsaicin (1 day before receiving 0.5μg artemin).

Figure 2A and 2B. Tactile allodynia measured by von Frey Hairs in animals from two experiments (A & B) injected with fibrosarcoma and treated with isotype (negative) control antibody (M2M180N) or M1M6977N or M1M6986N anti-mouse GFRα3 antibodies (n=8-11 per group). *p<.05, **p<.01, or ***p<.001 compared to isotype control at the same time point.

Figure 3A and 3B. Percent ipsilateral weight bearing in animals from two experiments (A & B) injected with fibrosarcoma and treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFRα3 antibodies (n=8-11 per group).

Figure 4A and 4B. Guarding scores in animals from two experiments (A & B) injected with fibrosarcoma cells and treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFRα3 antibodies (n=8-11 per group). **p<.01 compared to isotype control at the same time point.

Figure 5. Tactile allodynia measured by von Frey Hairs in animals injected with carcinoma and treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFRα3 antibodies (n=9-10 per group). *p<.05, **p<.01, or ***p<.001 compared to isotype (negative) control at the same time point.

Figure 6A and 6B. Percent ipsilateral weight bearing at two time points (A=11 days & B=18 days) injected with carcinoma and treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFRα3 antibodies (n=9-10 per group). *p<.05 compared to isotype control antibody by post hoc Dunnett's analysis.

Figure 7. Guarding scores in animals injected with carcinoma and treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFRα3 antibodies (n=9-10 per group). *p<.05, ***p<.001 compared to isotype control at the same time point.

Figure 8. Tactile allodynia measured by von Frey Hairs in animals with DMM treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFRα3 antibodies (n=10 per group). **p<.01 or ***p<.001 compared to isotype control at the same time point.

Figure 9. Cross-Competition Analysis of anti-GFRα3 Antibodies for Binding to Biotin-hGFRα3-mmH.

DETAILED DESCRIPTION

[0081] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0082] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described.

Definitions

[0083] "GFRα3," or "hGFRα3", as used herein, refers to the glycosylphosphatidylinositol (GPI)-anchored protein receptor for artemin, which belongs to the family of glial cell line derived neurotrophic factors (GDNF). It is one of the GDNF family receptor alpha proteins that, once bound to its ligand, artemin, mediates activation of the receptor tyrosine kinase

RET ("rearranged during transfection"). Four members of the GFRα family have been recognized to date, GFRα-1-4 (Lindsay RM et al., Neuron, (1996), 17:571-574; Airaksinen, MS, et al., Mol. Cell Neurosci., (1999), 13:313-325). GFRα3 is also known in the art as GDNF family receptor alpha 3 GPI-linked receptor, or glial cell line-derived neurotrophic factor receptor alpha-3. The expression "GFRα3," or "hGFRα3", or fragments thereof, as used herein, refers to the human GFRα3 protein or fragment thereof, unless specified as being from a non-human species, e.g. "mouse GFRα3", "rat GFRα3", or "monkey GFRα3". Moreover, "GFRα3," or "hGFRα3", as used herein, refers to human GFRα3 encoded by the nucleic acid sequence shown in SEQ ID NO: 374 (Genbank accession number NM_001496) and has the amino acid sequence as shown in SEQ ID NO: 375 (Genbank accession number NP_001487.2), or a biologically active fragment thereof. The signal sequence spans amino acid residues 1-31 of SEQ ID NO: 375, the mature protein spans amino acid residues 32-382 of SEQ ID NO: 375, whereas the C-terminal Pro region spans amino acid residues 383-400 of SEQ ID NO: 375. The GPI cleavage site is found at amino acid residue 374 of SEQ ID NO: 375 (asparagine). The amino acid sequence of human artemin is found in Genbank as accession number Q5T4W7 and the amino acid sequence of human artemin (from amino acids A108-G220 of accession number Q5T4W7) with a myc-myc-hexahistidine tag is shown as SEQ ID NO: 369 (with amino acid residues 114-141 of SEQ ID NO: 369 being the myc-myc hexahistidine tag).

[0084] Although GFRα3 is structurally and functionally similar to the other members of the GFRα family, GFRα3 is the most distantly related of the four family members. GFRα1 and GFRα2 share about 50% identity (Sanicola, M. et al., PNAS, USA, (1997), 94:6238-43; Klein, RD, et al., (1997), Nature, 387:717-21; Buj-Bello, A. et al., Nature (1997), 387:721-4; Baloh, RH, et al., Neuron, (1997), 18:793-802), while GFRα3 has only 32 and 37% identity, respectively, with these proteins (Masure, S. et al., Eur. J. Biochem., (1998), 251:622-30; Nomoto, S. et al., BBRC, (1998), 244:849-53). The amino acid sequence of mouse GFRα3 has the following Genbank Accession Number: NP_034410.3. The amino acid sequence of human GFRα1 has the following Genbank Accession Number: NP_005255.1 and is also found as SEQ ID NO: 376. The amino acid sequence of cynomolgus GFRα3 is shown in SEQ ID NO: 377 and the amino acid sequence of cynomolgus RET is shown in SEQ ID NO: 378.

[0085] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds *(i.e.,* "full antibody molecules"), as well as multimers thereof (e.g. IgM) or antigen-binding fragments thereof. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "V_H") and a heavy chain constant region (comprised of domains C_H1, C_H2 and C_H3). Each light chain is comprised of a light chain variable region ("LCVR or "V_L") and a light chain constant region (C_L). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In certain embodiments of the invention, the FRs of the anti-GFRα3 antibody (or antigen binding fragment thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0086] Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan et al. (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos et al. 2002 J Mol Biol 320:415-428).

[0087] CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s) thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

[0088] The fully-human anti-hGFRα3 antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are back-mutated to the corresponding germline residue(s) or to a conservative amino acid substitution (natural or non-natural) of the corresponding germline residue(s) (such sequence changes are referred to herein as "germline back-mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline back-mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the germline sequence. In other embodiments,

only certain residues are mutated back to the germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or to germline back-mutations within all framework regions FR1, FR2, FR3, FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. Furthermore, the antibodies of the present invention may contain any combination of two or more germline back-mutations within the framework and/or CDR regions, *i.e.,* wherein certain individual residues are mutated back to the germline sequence while certain other residues that differ from the germline sequence are maintained. Once obtained, antibodies and antigen-binding fragments that contain one or more germline back-mutations can be easily tested for one or more desired properties such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[0089] The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences. The anti-human GFRα3 antibodies of the invention may be designated as "anti-hGFRα3" or "anti-GFRα3".

[0090] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about $1x10^{-6}$ M or less (e.g., a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. An isolated antibody that specifically binds hGFRα3 may, however, exhibit cross-reactivity to other antigens such as GFRα3 molecules from other species. Moreover, multi-specific antibodies that bind to hGFRα3 and one or more additional antigens or a bi-specific that binds to two different regions of hGFRα3 are nonetheless considered antibodies that "specifically bind" hGFRα3, as used herein.

[0091] As used herein, the term "does not bind" to a specified target molecule (e.g. a particular GFRα3 peptide) means that the antibody, when tested for binding to the target molecule at 25°C in a Plasmon resonance assay, exhibits a K_D of greater than 500 nM, or if tested for binding to the target molecule at 25°C in an enzyme linked immunosorbent assay (ELISA) exhibits an EC_{50} of greater than 50 nM, or fails to exhibit any binding in either type of assay or equivalent thereof.

[0092] The term "high affinity" antibody refers to those mAbs having a binding affinity to hGFRα3 of at least 10^{-9} M; preferably 10^{-10} M; more preferably 10^{-11} M, even more preferably 10^{-12}M, as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

[0093] By the term "slow off rate", "Koff" or "kd" is meant an antibody that dissociates from hGFRα3 with a rate constant of 1×10^{-3} s^{-1} or less, preferably 1×10^{-4} s^{-1} or less, as determined by surface plasmon resonance, e.g., BIACORE™.

[0094] The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to hGFRα3.

[0095] The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety ("immunoconjugate"), such as an opioid, a COX-2 inhibitor, a local anesthetic, a cytokine antagonist, such as an IL-1 or IL-6 inhibitor, a second GFRα3 inhibitor, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a chemotherapeutic agent, or a radioisotope.

[0096] An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies (Abs) having different antigenic specificities (e.g., an isolated antibody that specifically binds hGFRα3, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than hGFRα3).

[0097] A "neutralizing antibody", as used herein (or an "antibody that neutralizes GFRα3 activity"), is intended to refer to an antibody whose binding to hGFRα3 results in inhibition of at least one biological activity of GFRα3. This inhibition of the biological activity of GFRα3 can be assessed by measuring one or more indicators of GFRα3 biological activity by one or more of several standard *in vitro* or *in vivo* assays known in the art (see examples below).

[0098] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

[0099] The term "K_D", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0100] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope"

also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[0101] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0102] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art (See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331). Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (See Gonnet et al., Science, (1992), 256:1443 45). A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0103] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. (See, e.g., Altschul et al. (1990) J. Mol. Biol. 215: 403 410 and (1997) Nucleic Acids Res. 25:3389 402).

[0104] In specific embodiments, the antibody or antibody fragment for use in the method of the invention may be monospecific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise an Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 mAbs; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 mAbs; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 mAbs. Variations on the bi-specific antibody format described above are

contemplated within the scope of the present invention.

[0105] By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0106] The term "functional pain syndrome(s)", refers to chronic symptom-based syndromes that affect up to 15% of the population worldwide. They are characterized by chronic pain and discomfort referred to in different regions of the body. No generally agreed-upon structural, inflammatory, or biochemical abnormalities have been identified that could fully explain the symptoms. Patients show a greatly reduced quality of life, yet treatment options are limited, and the development of novel therapeutic approaches has been disappointing. Some of the common disorders, which fall into this category, include chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, functional abdominal pain syndrome, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional rectal pain syndrome, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome, and Gulf War syndrome.

General Description

[0107] The glial cell line-derived neurotrophic factor related family includes glial cell line-derived neurotrophic factor (GDNF), neurturin (NRTN), persephin (PSPN), and artemin (ARTN). GDNF family proteins are differentially involved in the development and maintenance of sensory, enteric, sympathetic and parasympathetic neurons and a variety of non-neural tissues (Henderson, C.E., et al., (1994), Science 266:1062-1064; Kotzbauer, P.T. et al., (1996), Nature 384:467-470; Springer, J.E., et al. (1994), Exp. Neurol. 127:167-170; Schaar. D.G., et al., (1993), Exp. Neurol. 124:368-371). GDNF is an especially potent survival factor for dopaminergic, noradrenergic and spinal motor neurons (Yan, Q. et al. (1995), Nature, 373:341-344; Henderson, C.E., et al., (1994), Science, 266:1062-1064; Buj-Bello, A. et al., (1995), Neuron, 15:821-828). Other GDNF family growth members have functions outside the nervous system (Trupp, M. et al., (1995), J. Cell Biol. 130:137-148; Kotzbauer, P.T. et al., (1996), Nature 384:467-470; Springer, J.E., et al. (1994), Exp. Neurol. 127:167-170; Schaar. D.G., et al., (1993), Exp. Neurol. 124:368-371). For example, NRTN, ARTN, and PSPN are also expressed in the developing kidney. GDNF also has critical roles outside the nervous system in the regulation of kidney morphogenesis and spermatogenesis (Airaksinen, M.S. et al., (2002), Nature Reviews 3:383-392).

[0108] Each member of the GDNF family binds preferentially to (ie, is a ligand for) a glycosylphosphatidylinositol (GPI)-anchored protein receptor dynamically associated with the plasma membrane. The GDNF-family receptor alpha family is composed of four different receptors: GFRalpha1 (GFRα1, GDNFR-alpha); GFRalpha2 (GFRα2/TrnR2/GDNFR-beta/NTNR-alpha/RETL2); GFRalpha3 (GFRα3); and GFRalpha4 (GFRα4). GDNF binds preferentially to GFRα1, NRTN binds preferentially to GFRα2, ARTN binds preferentially to GFRα3 and PSPN binds preferentially to GFRα4 (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394).

[0109] GFRα2 is highly expressed in cortex, basal forebrain, and specific layers of the olfactory bulb, and poorly expressed in substantia nigra, cerebellum, and motor nuclei. GFRα3 is expressed in fetal and adult mouse nerves, sympathetic and sensory ganglia, intestine, heart, brain, lung and kidney. GFRα4 is expressed at low levels in different brain areas in the adult as well as in some peripheral tissues including testis and heart. While the GDNF family member binding preferences are shown above to be GDNF to GFRα1; neurturin to GFRα2; artemin to GFRα3; and persephin to GFRα4, the ligand receptor pairing is not stringent (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394). For example, GDNF binds to GFRα2 and GFRα3 with lower efficiencies than it binds to GFRα1.

[0110] The GDNF family ligands, typically but not exclusively, transmit their signals through multi-component complexes composed of a ligand, its GFR alpha receptor and the receptor tyrosine kinase, c-Ret. Ret is a common element of these ligand signaling complexes. Ret is a proto-oncogene that strongly activates anti-apoptotic signals through the activation of the phosphoinositol-3 kinases (PI3-K)/PDK/AKT(PKB) and the Ras/Raf/MEK/ERK pathways. Ret is also able to activate phospholipase C gamma (PLCgamma) which elevates intracellular calcium and facilitates activation of members of the conventional and novel protein kinase C (PKC) family. GDNF family ligand receptor complexes are not restricted to signaling through Ret. GDNF:GFRalpha1 can bind to NCAM in cells lacking RET and activate Fyn and FAK. Under some conditions GDNF:GFRalpha complexes directly activate src kinase.

[0111] In certain embodiments of the present invention, any one or more of the three globular cysteine-rich domains (1, 2, or 3) of GFRα3, or a fragment thereof, may be used to prepare antibodies that bind GFRα3 and inhibit its function, or inhibit its ability to bind its ligand, such as, artemin. In certain embodiments, an antibody of the invention specific for GFRα3 may bind to a ligand-binding domain on GFRα3, and as such, may block the binding of the ligand (artemin)-GFRα3 complex to RET. The full-length amino acid sequence of human GFRα3 is shown as SEQ ID NO: 375. The nucleic acid encoding human GFRα3 is shown in SEQ ID NO: 374. Domain 1 spans residues 44-124 of SEQ ID NO: 375; domain 2 spans residues 162-239 of SEQ ID NO: 375; domain 3 spans residues 248-340 of SEQ ID NO: 375. (See either SEQ

ID NO. 375 or Genbank NP_001487.2).

[0112] Any of these domains, 1, 2, or 3, or fragments derived therefrom, may be used to prepare antibodies that bind specifically to GFRα3 and inhibit its activity, or at least one function associated with GFRα3. In certain embodiments, the antibodies of the invention bind specifically to GFRα3 and may prevent signaling mediated by GFRα3. In certain embodiments, the antibodies that bind specifically to GFRα3 may prevent binding of GFRα3 to its ligand, such as artemin (Wang, X. et al. Structure, (2006), 14:1083-1092). In certain embodiments, the antibodies that bind specifically to GFRα3 may prevent activation of the RET receptor tyrosine kinase. In certain embodiments, the antibodies of the invention may bind specifically to GFRα3 without preventing activation of the RET receptor tyrosine kinase. In certain embodiments, the antibodies of the invention may bind specifically to GFRα3 and prevent signaling through RET, or through a mediator other than RET. In certain embodiments, the antibodies of the invention may be used to inhibit tumor cell growth/proliferation and as such, may be useful for treating certain cancers/malignancies, or the pain associated with such cancers/malignancies, or the pain associated with metastasis of such cancers/malignancies (See Tang, J-Z, et al. Mol Cancer Ther (2010), 9(6): 1697-1708; Kang, J. et al. Oncogene, (2009), 28:2034-2045; Ceyhan, G.O. et al. Annals of Surgery, (2006), 244(2):274-281; Banerjee, A., et al. Breast Cancer Res (2011), 13:R112; Pandey, V. et al., Endocrinology, (2010), 151(3):909-920; Kang, J. et al., Oncogene, (2010), 29:3228-3240; Li, S. et al. J Biomed Sci (2011), 18:24). In certain embodiments, antibodies that bind specifically to GFRα3 may be prepared using fragments of the above-noted regions, or peptides that extend beyond the designated regions by about 10 to about 50 amino acid residues from either, or both, the N or C terminal ends of the regions described herein. In certain embodiments, any combination of the above-noted regions or fragments thereof may be used in the preparation of GFRα3 specific antibodies. As noted above, the length, or the number of amino acid residues encompassing the three domains of hGFRα3 may vary by about ten to fifty amino acid residues extending from either, or both, the N terminal or C terminal end of the full length domain, or a fragment thereof, for preparation of anti-hGFRα3 specific antibodies.

Antigen-Binding Fragments of Antibodies

[0113] Unless specifically indicated otherwise, the term "antibody," as used herein, shall be understood to encompass antibody molecules comprising two immunoglobulin heavy chains and two immunoglobulin light chains (*i.e.,* "full antibody molecules") as well as antigen-binding fragments thereof. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to hGFRα3. An antibody fragment may include a Fab fragment, a $F(ab')_2$ fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and (optionally) constant domains. Such DNA is known and/or is readily available from, *e.g.,* commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0114] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.,* an isolated complementarity determining region (CDR)). Other engineered molecules, such as diabodies, triabodies, tetrabodies and minibodies, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0115] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H - V_H, V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0116] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H -C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L;
(viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker

region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.,* by disulfide bond(s)).

[0117] As with full antibody molecules, antigen-binding fragments may be mono-specific or multi-specific (e.g., bi-specific). A multi-specific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multi-specific antibody format, including the exemplary bi-specific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

Preparation of Human Antibodies

[0118] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human GFRα3.

[0119] Using VELOCIMMUNE™ technology or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to GFRα3 are initially isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0120] In general, the antibodies of the instant invention possess very high affinities, typically possessing K_D of from about 10^{-13} through about 10^{-8} M, or from about 10^{-12} through about 10^{-9} M when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

[0121] The anti-GFRα3 antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind human GFRα3. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the anti-GFRα3 antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an anti-GFRα3 antibody or antibody fragment that is essentially bioequivalent to an anti-GFRα3 antibody or antibody fragment of the invention.

[0122] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either as a single dose or as multiple doses. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

[0123] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0124] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0125] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0126] Bioequivalence may be demonstrated by *in vivo* and/or *in vitro* methods. Bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been

correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0127] Bioequivalent variants of anti-GFRα3 antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include anti-GFRα3 antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, e.g., mutations which eliminate or remove glycosylation.

Anti-GFRα3 Antibodies Comprising Fc Variants

[0128] According to certain embodiments of the present invention, anti-GFRα3 antibodies are provided comprising an Fc domain comprising one or more mutations, which enhance or diminish antibody binding to the FcRn receptor, e.g., at acidic pH as compared to neutral pH. For example, the present invention includes anti-GFRα3 antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.,* in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (*e.g.,* H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (*e.g.,* 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (*e.g.,* M428L) and 434S (*e.g.,* N434S) modification; a 428L, 259I (*e.g.,* V259I), and 308F (*e.g.,* V308F) modification; a 433K (*e.g.,* H433K) and a 434 (*e.g.,* 434Y) modification; a 252, 254, and 256 (*e.g.,* 252Y, 254T, and 256E) modification; a 250Q and 428L modification (*e.g.,* T250Q and M428L); and a 307 and/or 308 modification (*e.g.,* 308F or 308P).

[0129] For example, the present invention includes anti-GFRα3 antibodies comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (*e.g.,* T250Q and M248L); 252Y, 254T and 256E (*e.g.,* M252Y, S254T and T256E); 428L and 434S (*e.g.,* M428L and N434S); and 433K and 434F (*e.g.,* H433K and N434F). All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present invention.

Biological Characteristics of the Antibodies

[0130] In general, the antibodies of the present invention may function by binding to any one or more of the three globular cysteine-rich domains (1, 2, or 3) of hGFRα3. In certain embodiments, the antibodies of the present invention may bind to an epitope located on at least one of the cysteine-rich domains of hGFRα3. In certain embodiments, an antibody of the invention may bind to amino acid residues of domain 1 of GFRα3, ranging from about residue 44 to about residue 124 of SEQ ID NO: 375. In certain embodiments, an antibody of the invention may bind to amino acid residues of domain 2 of GFRα3, ranging from about residue 162 to about residue 239 of SEQ ID NO: 375. In certain embodiments, an antibody of the invention may bind to amino acid residues of domain 3 of GFRα3, ranging from about residue 248 to about residue 340 of SEQ ID NO: 375. In certain embodiments, the antibodies of the present invention may function by blocking or inhibiting GFRα3 activity by binding to a region in any one of the domains that acts as the ligand binding domain, thus preventing binding of the ligand, such as, artemin, to that site. In certain embodiments, an antibody of the invention may bind to the ligand binding site on one of the domains of GFRα3 and prevent subsequent binding of the artemin-GFRα3 complex to RET. In one embodiment, an antibody of the invention may bind to any one or more of the epitopes in the artemin-GFRα3 complex that may determine or play a role in the specificity between ligand and GFRα3, such as in the region ranging from residues 167-184 of SEQ ID NO: 375. In certain embodiments, an antibody of the invention may bind to one or more of the residues of domain 2 that are responsible for the specificity between artemin and GFRα3, for example, the amino acid residues at positions 167 (met), 176 (asp) and/or position 184 (glu), of SEQ ID NO: 375 and in so binding, may prevent ligand binding to its receptor, and subsequently may prevent signaling through the RET receptor tyrosine kinase, or through a signaling mediator or modulator other than RET. In certain embodiments, the antibodies of the invention may bind to the membrane bound form of GFRα3 or to the soluble form of GFRα3. In certain embodiments, the antibodies of the invention may bind GFRα3, but do not cross react with GFRα1, GFRα2, or GFRα4. In certain embodiments, the antibodies of the present invention may be bi-specific antibodies. The bi-specific antibodies of the invention may bind one epitope in one cysteine rich region of one domain and may also bind one cysteine-rich region in a second domain of hGFRα3. In certain embodiments, the bi-specific antibodies of the invention may bind to two different regions within the same domain. In certain embodiments, one arm

of a bi-specific antibody of the invention may bind to one cysteine rich region of one domain of hGFRα3 and the other arm may bind to RET, or to a modulator other than RET. In certain embodiments, the bispecific antibodies may bind one domain in GFRα3 and one domain in GFRα1 or GFRα2.

[0131] More specifically, the anti-GFRα3 antibodies of the invention may exhibit one or more of the following characteristics:

(i) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance;
(ii) demonstrates the ability to block about 50-100% of the binding of GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM;
(iii) demonstrates the ability to block about 20% to about 100% of the binding of GFRα3 to a solid support coated with a mixture of artemin and RET;
(iv) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM;
(v) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain;
(vi) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo;*
(vii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis;
(viii) does not cross-react with other GFR co-receptors for RET;
(ix) comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; or
(x) comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0132] Certain anti-GFRα3 antibodies of the present invention are able to inhibit or attenuate GFRα3 activity in an *in vitro* assay. The ability of the antibodies of the invention to bind to and inhibit the binding of GFRα3 to its ligand artemin alone or in the presence of RET may be measured using any standard method known to those skilled in the art, including binding assays, or assays to determine if the antibodies block the activation of RET by inhibiting the binding of GFRα3 to its receptor artemin, such as those described herein. Non-limiting, exemplary *in vitro* assays for measuring GFRα3 activity are illustrated in Examples 4 and 5, below.

[0133] The present invention includes anti-GFRα3 antibodies and antigen binding fragments thereof which bind to one or more of the cysteine rich globular domains of GFRα3, as shown in SEQ ID NO: 375, or to a fragment thereof. The antibodies specific for GFRα3 may contain no additional labels or moieties, or they may contain an N-terminal or C-terminal label or moiety. In one embodiment, the label or moiety is biotin. In a binding assay, the location of a label (if any) may determine the orientation of the peptide relative to the surface upon which the peptide is bound. For example, if a surface is coated with avidin, a peptide containing an N-terminal biotin will be oriented such that the C-terminal portion of the peptide will be distal to the surface.

[0134] In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds hGFRα3 and neutralizes hGFRα3 activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405; (iii) comprises any one or more of the heavy or light chain CDR1, CDR2, and CDR3 sequences depicted in Table 1 and combinations thereof; (iv) is specific for binding to and/or blocking GFRα3 activity without binding to and/or blocking other GFR alpha receptors, including GFRα1, GFRα2 and GFRα4; (v) demonstrates binding specificity for any one or more of the cysteine-rich globular domains of GFRα3; (vi) blocks activation of and signaling through the RET receptor tyrosine kinase; (vii) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo;* (viii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis; or inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain.

Epitope Mapping and Related Technologies

[0135] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques include, for example, a routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY) can be performed. Other methods include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol Biol 248:443-63), peptide cleavage analysis crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed

(Tomer (2000) Protein Science 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of the interface. As a result, amino acids that form part of the protein/antibody interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues that correspond to the specific amino acids with which the antibody interacts. *See, e.g.,* Ehring (1999) Analytical Biochemistry 267(2):252-259; Engen and Smith (2001) Anal. Chem. 73:256A-265A.

[0136] The term "epitope" refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0137] Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (See, e.g., US 2004/0101920). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce mAbs having the desired characteristics. MAP may be used to sort the antibodies of the invention into groups of antibodies binding different epitopes.

[0138] In certain embodiments, the anti-GFRα3 antibody or antigen-binding fragment of an antibody binds an epitope within at least one of the GFRα3 cysteine rich domains 1, 2, or 3, or a fragment thereof, wherein domain 1 ranges from about residue number 44 to about residue number 124 of SEQ ID NO: 375; domain 2 ranges from about residue number 162 to about residue number 239 of SEQ ID NO: 375; domain 3 ranges from about residue number 248 to about residue number 340 of SEQ ID NO: 375.

[0139] In certain embodiments, the anti-GFRα3 antibody or antigen-binding fragment of an antibody binds an epitope within domain 1, or a fragment thereof, of human GFRα3.

[0140] In certain embodiments, the anti-GFRα3 antibody or antigen-binding fragment of an antibody binds an epitope within domain 2, or a fragment thereof, of human GFRα3.

[0141] In certain embodiments, the anti-GFRα3 antibody or antigen-binding fragment of an antibody binds an epitope within domain 3, or a fragment thereof, of human GFRα3.

[0142] In certain embodiments, the antibody or antibody fragment binds an epitope, which includes more than one of the enumerated epitopes of GFRα3 within domain 1, 2, or 3, and/or within two different domains (for example, epitopes within the 1 and 2 domains, or within the 2 and 3 domains, or within the 1 and 3 domains).

[0143] In certain embodiments, the antibody is a bi-specific antibody that binds one epitope within one domain of GFRα3 and another epitope within a different domain of GFRα3. In one embodiment, the antibody is a bi-specific antibody that binds one epitope in domain 1 of GFRα3 and another epitope in domain 2 of GFRα3. In one embodiment, the antibody is a bi-specific antibody that binds one epitope in domain 1 of GFRα3 and another epitope within domain 3 of GFRα3. In one embodiment, the antibody is a bi-specific antibody that binds one epitope in domain 2 of GFRα3 and another epitope within domain 3 of GFRα3.

[0144] The present invention includes anti-GFRα3 antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein (e.g., H4H2207N, H4H2212N, H4H2236N3, H4H2243N2, H4H2210N, H4H2234N, H4H2291S, H4H2292S, H4H2293P, H4H2294S, H4H2295S, H4H2296S, H4H2341S, H4H2342P, H4H2344S, H4H2345S, H4H2346S, H4H2350P, H4H2352S, H4H2354S, H4H2355S, H4H2357S, H4H2364S, H1M2243N and H1M2236N). Likewise, the present invention also includes anti-GFRα3 antibodies that compete for binding to GFRα3 or a GFRα3 fragment with any of the specific exemplary antibodies described herein.

[0145] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-GFRα3 antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-GFRα3 antibody of the invention, the reference antibody is allowed to bind to a GFRα3 protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the GFRα3 molecule is assessed. If the test antibody is able to bind to GFRα3 following saturation binding with the reference anti-GFRα3 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-GFRα3 antibody. On the other hand, if the test antibody is not able to bind to the GFRα3 molecule following saturation binding with the reference anti-GFRα3 antibody, then the test antibody may bind to the same epitope as the epitope bound by

the reference anti-GFRα3 antibody of the invention.

[0146] To determine if an antibody competes for binding with a reference anti-GFRα3 antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a GFRα3 molecule under saturating conditions followed by assessment of binding of the test antibody to the GFRα3 molecule. In a second orientation, the test antibody is allowed to bind to a GFRα3 molecule under saturating conditions followed by assessment of binding of the reference antibody to the GFRα3 molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the GFRα3 molecule, then it is concluded that the test antibody and the reference antibody compete for binding to GFRα3. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the identical epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

[0147] Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990 50:1495-1502). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0148] Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

Species Selectivity and Species Cross-Reactivity

[0149] According to certain embodiments of the invention, the anti-GFRα3 antibodies bind to human GFRα3 but not to GFRα3 from other species. Alternatively, the anti-GFRα3 antibodies of the invention, in certain embodiments, bind to human GFRα3 and to GFRα3 from one or more non-human species. For example, the anti-GFRα3 antibodies of the invention may bind to human GFRα3 and may bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgus, marmoset, rhesus or chimpanzee GFRα3.

Immunoconjugates

[0150] The invention encompasses a human anti-GFRα3 monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an agent that is capable of reducing pain and/or inflammation, a chemotherapeutic drug, or a radioisotope. The type of therapeutic moiety that may be conjugated to the anti-GFRα3 antibody will take into account the condition to be treated and the desired therapeutic effect to be achieved. For example, for treating acute or chronic pain, an agent such as an NSAID, an opioid, or a Cox-2 inhibitor, or a local anesthetic agent, or a second GFRα3 inhibitor may be conjugated to the GFRα3 antibody. Alternatively, if the desired therapeutic effect is to treat the inflammation associated with a painful condition, it may be advantageous to conjugate an anti-inflammatory agent to the anti-GFRα3 antibody, such as, but not limited to, celecoxib, or a cytokine antagonist, such as an IL-1 or an IL-6 inhibitor. If the condition to be treated is a cancerous condition, it may be beneficial to conjugate a chemotherapeutic drug, or a radioisotope to the GFRα3 antibody. Examples of suitable agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Multi-specific Antibodies

[0151] The antibodies of the present invention may be mono-specific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, *e.g.,* Tutt et al., 1991, J. Immunol. 147:60-69; Kufer et al., 2004, Trends Biotechnol. 22:238-244. The anti- GFRα3 antibodies of the present invention can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multi-specific antibody with a second binding specificity. For example, the present invention includes bi-specific antibodies wherein one arm of an immunoglobulin is specific for human GFRα3 or a fragment thereof, and the other arm of the immunoglobulin

is specific for a second therapeutic target or is conjugated to a therapeutic moiety. In certain embodiments of the invention, one arm of an immunoglobulin is specific for an epitope on one domain of hGFRα3 or a fragment thereof, and the other arm of the immunoglobulin is specific for an epitope on a second domain of hGFRα3. In certain embodiments, one arm of an immunoglobulin is specific for one epitope on one domain of hGFRα3 and the other arm is specific for a second epitope on the same domain of hGFRα3.

[0152] An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

Therapeutic Administration and Formulations

[0153] The invention provides therapeutic compositions comprising the anti-GFRα3 antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0154] The dose of antibody may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibody of the present invention is used for treating pain associated with GFRα3 activity in various conditions and diseases, wherein the condition or disease results in acute or chronic pain, inflammatory pain, neuropathic pain, and the like, in an adult patient, it is advantageous to intravenously administer the antibody of the present invention normally at a single dose of about 0.01 to about 20 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted.

[0155] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al. (1987) J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0156] The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see, for example, Langer (1990) Science 249:1527-1533).

[0157] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose.

[0158] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80,

HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0159] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0160] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousands Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.) and the HUMIRA™ Pen (Abbott Labs, Abbott Park, IL), to name only a few.

[0161] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Therapeutic Uses of the Antibodies

[0162] The antibodies of the invention are useful for the treatment, prevention and/or amelioration of any disease, disorder, or condition associated with GFRα3 activity, or for amelioration of at least one symptom associated with the disease, disorder, or condition, or for alleviating the pain associated with such disease, disorder, or condition. Exemplary conditions, diseases and/or disorders, and/or the pain associated with such conditions, diseases, or disorders, that can be treated with the anti-GFRα3 antibodies of the present invention include acute, chronic, neuropathic, or inflammatory pain, arthritis, interstitial cystitis, pancreatitis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epileptic conditions, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, irritable bowel syndrome, inflammatory bowel syndrome, fecal urgency, incontinence, rectal hypersensitivity, visceral pain, osteoarthritis pain, gout, post-herpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, breakthrough pain, post-surgical pain, cancer pain, including pain associated with bone cancer or pancreatic cancer.

[0163] Other conditions treatable by the therapeutic methods of the invention included hereditary erythromelalgia, rhinitis, prostate cancer, breast cancer, bone cancer, cervical cancer, or bladder disorders. The antibodies of the invention or antigen-binding fragments thereof may also be used to treat the following conditions: non-malignant acute, chronic, or fracture bone pain; rheumatoid arthritis, spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; visceral pain, including, abdominal; pancreatic; chronic headache pain; tension headache, including, cluster headaches; diabetic neuropathy; HIV-associated neuropathy; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome (CRPS); phantom pain; intractable pain; musculoskeletal pain; joint pain; acute gout pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; burn and trauma pain; endometriosis; herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis pain; leprosy pain; Behcet's disease

pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; Fabry's disease pain; bladder and urogenital disease; hyperactivity bladder.

[0164] In one embodiment the antibodies of the invention may be used to treat a functional pain syndrome, wherein the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome (CFS), abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome.

[0165] The antibodies of the invention or antigen-binding fragments thereof may also be used to inhibit tumor cell growth/proliferation or metastasis of tumor cells. Accordingly, in certain embodiments, the antibodies of the invention or antigen-binding fragments thereof, may be used to treat a cancer, including, but not limited to, endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, non-small cell lung cancer, brain cancer, a leukemia, a lymphoma, bone cancer, or pain associated with metastasis of a cancer, for example, metastasis of a cancer to the bone. (See Tang, J-Z, et al. Mol Cancer Ther (2010), 9(6): 1697-1708; Kang, J. et al. Oncogene, (2009), 28:2034-2045; Ceyhan, G.O. et al. Annals of Surgery, (2006), 244(2):274-281; Banerjee, A., et al. Breast Cancer Res (2011), 13:R112; Pandey, V. et al., Endocrinology, (2010), 151(3):909-920; Kang, J. et al., Oncogene, (2010), 29:3228-3240; Li, S. et al. J Biomed Sci (2011), 18:24).

[0166] The antibodies of the present invention are also useful for treating or preventing cancer-associated pain. "Cancer-associated pain" includes, e.g., bone cancer pain, including pain from cancer that has metastasized to bone (e.g., breast cancer, prostate cancer, lung cancer, sarcoma, kidney cancer, multiple myeloma, etc.). "Cancer-associated pain" also includes pain more generally associated with cancerous conditions such as, e.g., renal cell carcinoma, pancreatic carcinoma, breast cancer, head and neck cancer, prostate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, malignant mesothelioma, multiple myeloma, ovarian cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, or melanoma. The antibodies of the present invention are also useful for treating or preventing pain caused by or associated with cancer therapy or anti-cancer medical treatments, e.g., chemotherapy-induced neuropathic pain such as pain caused by or associated with treatment with paclitaxel (Taxol™), docetaxel (Taxotere®); nitrosourea, cyclophosphamide, doxorubicin, epirubicin, 5-fluorouracil, topotecan, irinotecan, carmustine, estramustine, and platinum-based chemotherapeutic compounds, such as cisplatin, carboplatin, and iproplatin.

Combination Therapies

[0167] Combination therapies may include an anti-hGFRα3 antibody of the invention and, for example, another GFRα3 antagonist (e.g., anti-GFRα3 antibody or small molecule inhibitor of GFRα3); a COX-2 inhibitor; a local anesthetic; an NMDA modulator; a cannabinoid receptor agonist; a P2X family modulator; a VR1 antagonist; a substance P antagonist; an inhibitor of a voltage-gated sodium channel (Na_v), for example, a $Na_v1.7$ antagonist, or a $Na_v1.8$ antagonist (e.g., anti-$Na_v1.7$ or anti-$Na_v1.8$ antibody or small molecule inhibitor), a $Na_v1.9$ antagonist (*e.g.,* anti-$Na_v1.9$ antibody or small molecule inhibitor of $Na_v1.9$); a calcium channel inhibitor; a potassium channel inhibitor; a cytokine inhibitor or cytokine receptor antagonist (*e.g.*, an interleukin-1 (IL-1) inhibitor (such as rilonacept ("IL-1 trap"; Regeneron) or anakinra (KINERET®, Amgen), a small molecule IL-1 antagonist, or an anti-IL-1 antibody); an IL-18 inhibitor (such as a small molecule IL-18 antagonist or an anti-IL-18 antibody); an IL-6 or IL-6R inhibitor (such as a small molecule IL-6 antagonist, an anti-IL-6 antibody or an anti-IL-6 receptor antibody); an antiepileptic/anti-convulsant drug (*e.g.,* gabapentin, pregabalin); a nerve growth factor (NGF) inhibitor (*e.g.,* a small molecule NGF antagonist or an anti-NGF antibody); an inhibitor of BDNF, TrkA, TrkB or p75; an opioid; morphine; low dose cochicine; aspirin or another NSAID; steroids (e.g., prednisone, methotrexate, etc.); low dose cyclosporine A; a selective serotonin reuptake inhibitor (SSRI); a serotonin norepinephrine reuptake inhibitor (SNRI); a tricyclic; a tumor necrosis factor (TNF) or TNF receptor inhibitor (e.g., a small molecule TNF or TNFR antagonist or an anti-TNF or TNFR antibody); an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis); a RET inhibitor; an inhibitor of a GDNF family ligand; an inhibitor of GFRα1, GFRα2 or GFRα4; an inhibitor of an acid sensing ion channel (*e.g.* ASIC1 or ASIC3; uric acid synthesis inhibitors (e.g., allopurinol); uric acid excretion promoters (e.g., probenecid, sulfinpyrazone, benzbromarone, etc.); an inhibitor of a prekineticin receptor (PROK1 and PROK2); other inflammatory inhibitors (*e.g.,* inhibitors of caspase-1, p38, IKK1/2, CTLA-4Ig, etc.); and/or corticosteroids.

Administration Regimens

[0168] According to certain embodiments of the present invention, multiple doses of an anti-GFRα3 antibody may be administered to a subject over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a subject multiple doses of an anti-GFRα3 antibody. As used herein, "sequentially administering" means that each dose of anti-GFRα3 antibody is administered to the subject at a different point in time, e.g.,

on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an anti-GFRα3 antibody, followed by one or more secondary doses of the anti-GFRα3 antibody, and optionally followed by one or more tertiary doses of the anti-GFRα3 antibody.

[0169] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the anti-GFRα3 antibody. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of anti-GFRα3 antibody, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of anti-GFRα3 antibody contained in the initial, secondary and/or tertiary doses varies from one another (*e.g.,* adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (*e.g.,* 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (*e.g.,* "maintenance doses").

[0170] In one exemplary embodiment of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (*e.g.,* 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of anti- GFRα3 antibody, which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0171] The methods according to this aspect of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of an anti-GFRα3 antibody. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.,* 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.,* 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0172] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient.

Diagnostic Uses of the Antibodies

[0173] The anti-GFRα3 antibodies of the present invention may also be used to detect and/or measure GFRα3 in a sample, *e.g.,* for diagnostic purposes. For example, an anti-GFRα3 antibody, or fragment thereof, may be used to diagnose a condition or disease characterized by aberrant expression (*e.g.,* over-expression, under-expression, lack of expression, etc.) of GFRα3. Exemplary diagnostic assays for GFRα3 may comprise, *e.g.,* contacting a sample, obtained from a patient, with an anti-GFRα3 antibody of the invention, wherein the anti-GFRα3 antibody is labeled with a detectable label or reporter molecule. Alternatively, an unlabeled anti-GFRα3 antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure GFRα3 in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0174] Samples that can be used in GFRα3 diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of GFRα3 protein, or fragments thereof, under normal or pathological conditions. Generally, levels of GFRα3 in a particular sample obtained from a healthy patient (*e.g.,* a patient not afflicted with a disease or condition associated with abnormal GFRα3 levels or activity) will be measured to initially establish a baseline, or standard, level of GFRα3. This baseline level of GFRα3 can then be compared against the levels of GFRα3 measured in samples obtained from individuals suspected of having a GFRα3 related disease or condition, or pain associated with such disease or condition.

EXAMPLES

[0175] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Generation of Human Antibodies to Human GFRα3

[0176] An immunogen comprising any one of the GFRα3 peptides having amino acid sequences shown as SEQ ID NOS: 370, 371, 372 and 373, or fragments thereof, may be utilized to generate antibodies to human GFRα3. These peptides are conjugated to a carrier, for example, KLH, then administered with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse comprising DNA encoding human Immunoglobulin heavy and kappa light chain variable regions. The antibody immune response is monitored by a GFRα3-specific immunoassay. When a desired immune response is achieved, splenocytes are harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines are screened and selected to identify cell lines that produce GFRα3-specific antibodies. Using this technique several anti-GFRα3 chimeric antibodies (*i.e.,* antibodies possessing human variable domains and mouse constant domains) were obtained. The anti-GFRα3 antibodies generated using this method were designated H1M2207N, H1M2212N, H1M2236N, H1M2236N3, H1M2243N, H1M2243N2, H1M2210N and H1M2234N.

[0177] Anti-GFRα3 antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. 2007/0280945A1. Using this method, several fully human anti-GFRα3 antibodies *(i.e.,* antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H4H2207N, H4H2212N, H4H2236N, H4H2243N, H4H2210N, H4H2234N, H4H2291S, H4H2292S, H4H2293P, H4H2294S, H4H2295S, H4H2296S, H4H2341S, H4H2342P, H4H2344S, H4H2345S, H4H2346S, H4H2350P, H4H2352S, H4H2354S, H4H2355S, H4H2357S and H4H2364S.

[0178] The biological properties of the exemplary anti-GFRα3 antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2. Heavy and Light Chain Variable Region Amino Acid Sequences

[0179] Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected anti-GFRα3 antibodies and their corresponding antibody identifiers. Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (e.g. "H4H", "H1M, "H2M"), followed by a numerical identifier (e.g. "2207" as shown in Table 1), followed by a "P", "S", or "N" suffix. Thus, according to this nomenclature, an antibody may be referred to as, e.g. "H4H2207N". The H4H, H1M, and H2M prefixes on the antibody designations used herein indicate the particular Fc region of the antibody. For example, an "H2M" antibody has a mouse IgG2 Fc, whereas an "H4H" antibody has a human IgG4 Fc. As will be appreciated by a person of ordinary skill in the art, an H1M or H2M antibody can be converted to an H4H antibody, and vice versa, but in any event, the variable domains (including the CDRs), which are indicated by the numerical identifiers shown in Table 1, will remain the same. Antibodies having the same numerical antibody designation, but differing by a letter suffix of N, B, S or P refer to antibodies having heavy and light chains with identical CDR sequences but with sequence variations in regions that fall outside of the CDR sequences *(i.e.,* in the framework regions). Thus, N, B, S and P variants of a particular antibody have identical CDR sequences within their heavy and light chain variable regions but differ from one another within their framework regions.

Table 1

	AMINO ACID SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
H4H2207N	2	4	6	8	10	12	14	16
H4H2212N	18	20	22	24	26	28	30	32
H4H2236N3	34	36	38	40	42	44	46	48
H4H2243N2	50	52	54	56	58	60	62	64

(continued)

	AMINO ACID SEQ ID NOs:							
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**
H4H2210N	66	68	70	72	74	76	78	80
H4H2234N	82	84	86	88	90	92	94	96
H4H2291S	98	100	102	104	106	108	110	112
H4H2292S	114	116	118	120	122	124	126	128
H4H2293P	130	132	134	136	138	140	142	144
H4H2294S	146	148	150	152	154	156	158	160
H4H2295S	162	164	166	168	170	172	174	176
H4H2296S	178	180	182	184	186	188	190	192
H4H2341S	194	196	198	200	202	204	206	208
H4H2342P	210	212	214	216	218	220	222	224
H4H2344S	226	228	230	232	234	236	238	240
H4H2345S	242	244	246	248	250	252	254	256
H4H2346S	258	260	262	264	266	268	270	272
H4H2350P	274	276	278	280	282	284	286	288
H4H2352S	290	292	294	296	298	300	302	304
H4H2354S	306	308	310	312	314	316	318	320
H4H2355S	322	324	326	328	330	332	334	336
H4H2357S	338	340	342	344	346	348	350	352
H4H2364S	354	356	358	360	362	364	366	368
H1M2243N	381	383	385	387	389	391	393	395
H1M2236N	397	399	401	403	405	407	409	411

Example 2. Variable Gene Utilization Analysis

[0180] To analyze the structure of antibodies produced, the nucleic acids encoding antibody variable regions were cloned and sequenced. From the nucleic acid sequence and predicted amino acid sequence of the antibodies, gene usage was identified for each Heavy Chain Variable Region (HCVR) and Light Chain Variable Region (LCVR). Table 2 sets forth the gene usage for selected antibodies in accordance with the invention.

Table 2

	HCVR			LCVR	
AbPID	V_H	D_H	J_H	V_K	J_K
kH1M2207N	3-9	6-6	4	1-5	2
H1M2212N	3-23	1-26	4	4-1	1
H1M2236N	3-23	3-3	6	1-16	4
H4H2236N3	3-23	3-3	6	1-16	4
H1M2243N	1-18	6-6	6	1-16	3
H4H2243N2	1-18	6-6	6	1-16	3
H2M2210N	3-23	1-20	3	3-20	4

(continued)

AbPID	HCVR			LCVR	
	V_H	D_H	J_H	V_K	J_K
H2M2234N	3-23	5-18	4	4-1	1
H4H2291S	3-23	6-6	6	1D-12	4
H4H2292S	3-33	1-7	3	1-39	3
H4H2293P	3-33	2-15	3	1-39	2
H4H2294S	3-23	6-6	6	1D-12	3
H4H2295S	3-23	6-6	6	1D-12	3
H4H2296S	3-23	6-6	6	1D-12	3
H4H2341S	1-69	3-10	5	1-39	5
H4H2342P	3-23	1-26	4	1-27	3
H4H2344S	3-33	2-15	3	1-39	2
H4H2345S	3-9	1-26	4	1-27	4
H4H2346S	3-33	2-15	3	1-39	2
H4H2350P	4-59	2-21	4	1-9	1
H4H2352S	1-18	3-3	3	3-20	2
H4H2354S	3-33	2-15	3	1-39	2
H4H2355S	3-23	6-6	4	1-5	4
H4H2357S	3-23	3-10	6	1-12	4
H4H2364S	3-23	6-6	6	1D-12	3

Example 3. Binding Affinities of GFRα3 Antibodies

[0181] Binding associative and dissociative rate constants (k_a and k_d, respectively) and calculated equilibrium dissociation constants and dissociative half-lives (K_D and $t_{1/2}$, respectively) for antigen binding to anti-GFRα3 antibodies were determined using a real-time surface plasmon resonance biosensor (Biacore T200) assay at 25°C and 37°C. Antibodies were tested for binding to human GFRα3 expressed with either a C-terminal myc-myc-hexahistidine tag (hGFRα3-mmh; SEQ ID: 370, a C-terminal hFc tag (hGFRα3-hFc; SEQ ID:371), or a C-terminal mFc tag (hGFRα3-mFc; SEQ ID:372), as well as monkey GFRa3 expressed with a C-terminal myc-myc-hexahistidine tag (MfGFRα3-mmh; SEQ ID:373). Anti-GFRα3 antibodies were captured on either a goat anti-mouse IgG polyclonal antibody (GE Healthcare, # BR-1008-38) or a mouse anti-human IgG monoclonal antibody (GE Healthcare, #BR-1008-39) surface created through direct amine coupling to a Biacore CM5 sensor chip. Kinetic experiments were carried out using HBS-EP (10mM HEPES, 150mM NaCl, 3mM EDTA, 0.05% Surfactant P20, at pH 7.4) or PBS buffer containing 0.05% v/v surfactant P20 as both the running buffer and the sample buffer. Binding to human GFRα3-mmh or monkey GFRα3-mmh was evaluated by injecting several concentrations ranging from 200 to 7.4 nM (3-fold dilutions) across the captured antibody surface. Binding to human GFRα3-mFc or human GFRα3-hFc was evaluated by injecting several concentrations ranging from 100 to 3.7 nM (3-fold dilutions) across the captured antibody surface. Antibody-antigen association was monitored for up to 4 minutes, while dissociation in buffer was monitored for up to 20 minutes. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0c curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives ($t_{1/2}$) were calculated from the kinetic rate constants as: K_D (M) = k_d / k_a and $t_{½}$ (min) = [ln2/(60*k_d)].

[0182] As shown in Table 3, at 25°C, all 25 anti-GFRα3 antibodies bound to hGFRα3-mmh with K_D values ranging from 82.0pM to 29.7nM. At 37°C, all 25 anti-GFRα3 antibodies bound to hGFRα3-mmh with K_D values ranging from 118pM to 47.3nM. As shown in Table 4, at 25°C, all 23 anti-GFRα3 antibodies bound to MfGFRα3-mmh with K_D values ranging from 2.90pM to 97.2nM. At 37°C, all 23 anti-GFRα3 antibodies bound to MfGFRα3-mmh with K_D values ranging from 11.7pM to 145nM. As shown in Table 5, at 25°C and 37°C, 6 of the 23 anti-GFRα3 antibodies were tested for binding to hGFRα3-hFc, while the other 17 antibodies were tested for binding to hGFRα3-mFc. At 25°C, the 6 anti-

GFRα3 antibodies tested for binding to hGFRα3-hFc bound with K_D values ranging from 7.50pM to 220pM. At 37°C, the 6 anti-GFRα3 antibodies tested for binding to hGFRα3-hFc bound with K_D values ranging from 41.3pM to 531 pM. At 25°C, the 17 anti-GFRα3 antibodies tested for binding to hGFRα3-mFc bound with K_D values ranging from 0.467pM to 58.4pM. At 37°C, the 17 anti-GFRα3 antibodies tested for binding to hGFRα3-mFc bound with K_D values ranging from 13.2pM to 106pM.

Table 3: Kinetics of hGFRα3-mmH binding to different anti-GFRα3 antibodies at 25°C and at 37°C

	25°C				37°C			
AbPID	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**$t_{½}$ (min)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**$t_{½}$ (min)**
H4H2291 S	4.18E+05	1.64E-04	3.93E-10	70	5.58E+05	3.23E-04	5.80E-10	36
H4H2292S	1.08E+05	5.19E-05	4.83E-10	223	1.28E+05	2.49E-04	1.94E-09	46
H4H2293P	5.81E+05	1.27E-04	2.19E-10	91	7.81E+05	2.44E-04	3.13E-10	47
H4H2294S	5.63E+05	7.99E-05	1.42E-10	145	7.73E+05	2.61 E-04	3.38E-10	44
H4H2295S	4.75E+05	2.56E-04	5.40E-10	45	6.69E+05	1.19E-03	1.77E-09	10
H4H2296S	5.63E+05	1.87E-04	3.32E-10	62	7.65E+05	6.14E-04	8.02E-10	19
H4H2341 S	1.59E+05	2.67E-04	1.68E-09	43	2.48E+05	7.37E-04	2.98E-09	16
H4H2342P	1.86E+05	2.04E-04	1.10E-09	57	3.30E+05	6.71E-04	2.03E-09	17
H4H2344S	1.83E+05	2.40E-04	1.31E-09	48	2.80E+05	7.24E-04	2.58E-09	16
H4H2345S	1.09E+05	3.23E-03	2.97E-08	4	1.84E+05	8.70E-03	4.73E-08	1
H4H2346S	1.86E+05	7.99E-05	4.30E-10	145	4.19E+05	5.89E-04	1.41E-09	20
H4H2350P	1.03E+05	2.07E-04	2.01E-09	56	1.34E+05	1.28E-03	9.61E-09	9
H4H2352S	7.09E+05	5.81E-05	8.20E-11	199	1.18E+06	1.39E-04	1.18E-10	83
H4H2354S	2.00E+05	1.10E-04	5.48E-10	105	2.81 E+05	6.49E-04	2.31E-09	18
H4H2355S	1.86E+05	1.52E-04	8.21E-10	76	2.81 E+05	1.23E-03	4.37E-09	9
H4H2357S	2.30E+05	5.57E-04	2.42E-09	21	2.95E+05	2.10E-03	7.12E-09	6
H4H2364S	3.53E+05	3.67E-05	1.04E-10	315	3.38E+05	2.73E-04	8.09E-10	42
H1M2207N	5.61E+04	9.00E-04	1.60E-08	13	1.33E+05	1.44E-03	1.08E-08	8
H2aM2210N	6.73E+04	8.63E-04	1.28E-08	13	2.12E+05	3.35E-03	1.58E-08	3
H1M2212N	8.00E+05	1.58E-04	1.97E-10	73	1.02E+06	3.03E-04	2.97E-10	38
H2aM2234N	6.57E+05	7.11E-04	1.08E-09	16	7.93E+05	2.72E-03	3.43E-09	4
H1M2236N	7.60E+05	2.08E-04	2.75E-10	56	1.03E+06	5.50E-04	5.32E-10	21
H4H2236N3	9.22E+05	2.33E-04	2.53E-10	50	1.96E+06	7.48E-04	3.82E-10	15
H4H2243N2	2.67E+05	7.80E-04	2.92E-09	15	4.69E+05	2.44E-03	5.20E-09	5
H1 M2243N	1.28E+05	2.61E-04	2.04E-09	44	1.37E+05	5.95E-04	4.35E-09	19

Table 4: Kinetics of MfGFRα3-mmH binding to different anti-GFRα3 antibodies at 25°C and at 37°C

	25°C				37°C			
AbPID	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**$t_{½}$ (min)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**$t_{½}$ (min)**
H4H2291 S	1.51E+05	2.79E-04	1.85E-09	41	3.57E+05	6.93E-04	1.94E-09	17
H4H2292S	7.76E+04	1.22E-04	1.57E-09	95	8.95E+04	1.95E-04	2.18E-09	59
H4H2293P	2.90E+05	4.17E-05	1.44E-10	277	4.41E+05	1.58E-04	3.58E-10	73

(continued)

	25°C				37°C			
AbPID	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**$t_{½}$ (min)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**$t_{½}$ (min)**
H4H2294S	3.25E+05	2.04E-04	6.27E-10	57	4.33E+05	9.74E-04	2.25E-09	12
H4H2295S	1.83E+05	9.73E-04	5.32E-09	12	2.76E+05	5.61 E-03	2.04E-08	2
H4H2296S	1.93E+05	6.51E-04	3.37E-09	18	2.77E+05	2.85E-03	1.03E-08	4
H4H2341 S	9.38E+04	1.30E-04	1.39E-09	89	1.44E+05	5.08E-04	3.53E-09	23
H4H2342P	9.37E+04	5.50E-04	5.87E-09	21	1.50E+05	1.66E-03	1.11 E-08	7
H4H2344S	1.04E+05	1.15E-04	1.10E-09	101	1.61E+05	5.75E-04	3.57E-09	20
H4H2345S	9.75E+04	2.79E-03	2.87E-08	4	1.34E+05	3.53E-03	2.63E-08	3
H4H2346S	1.08E+05	5.98E-05	5.56E-10	193	1.53E+05	5.11E-04	3.34E-09	23
H4H2350P	6.47E+04	1.11E-04	1.71E-09	104	7.48E+04	8.96E-04	1.20E-08	13
H4H2352S	3.45E+05	1.00E-06	2.90E-12	11550	5.57E+05	6.53E-05	1.17E-10	177
H4H2354S	1.09E+05	6.23E-05	5.74E-10	185	1.57E+05	4.35E-04	2.78E-09	27
H4H2355S	1.05E+05	6.78E-05	6.49E-10	170	1.73E+05	9.13E-04	5.29E-09	13
H4H2357S	1.40E+05	3.15E-04	2.26E-09	37	1.72E+05	1.35E-03	7.86E-09	9
H4H2364S	1.22E+05	1.30E-04	1.06E-09	89	1.68E+05	8.61E-04	5.14E-09	13
H1M2207N	3.99E+04	3.88E-03	9.72E-08	3	4.58E+04	6.63E-03	1.45E-07	2
H2aM2210N	4.16E+04	1.20E-03	2.89E-08	10	8.09E+04	6.18E-03	7.64E-08	2
H1M2212N	3.84E+05	1.12E-04	2.93E-10	103	8.84E+05	2.60E-04	2.94E-10	44
H2aM2234N	4.27E+05	5.71E-04	1.34E-09	20	4.29E+05	2.11E-03	4.91 E-09	5
H1M2236N	2.96E+05	2.86E-04	9.70E-10	40	4.34E+05	1.12E-03	2.58E-09	10
H1 M2243N	6.46E+04	6.58E-04	1.02E-08	18	5.02E+04	2.75E-03	5.47E-08	4

Table 5: Kinetics of hGFRα3-hFc or hGFRα3-mFc binding to different anti-GFRα3 antibodies at 25°C and at 37°C

	25°C				37°C			
AbPID	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**t½ (min)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**t½ (min)**
H4H2291S	1.03E+06	4.78E-06	4.63E-12	2417	1.33E+06	3.84E-05	2.89E-11	301
H4H2292S	5.34E+05	1.00E-06	1.87E-12	11550	5.96E+05	2.57E-05	4.32E-11	449
H4H2293P	1.22E+06	1.93E-06	1.59E-12	5988	1.71E+06	5.13E-05	2.99E-11	225
H4H2294S	1.22E+06	5.63E-06	4.63E-12	2052	1.66E+06	3.46E-05	2.09E-11	334
H4H2295S	1.08E+06	1.69E-06	1.57E-12	6822	1.62E+06	4.88E-05	3.01E-11	237
H4H2296S	1.24E+06	4.17E-06	3.37E-12	2770	1.61 E+06	4.74E-05	2.94E-11	244
H4H2341S	5.96E+05	1.00E-06	1.68E-12	11550	9.61E+05	7.58E-05	7.89E-11	152
H4H2342P	6.61 E+05	1.00E-06	1.51E-12	11550	1.21E+06	4.28E-05	3.54E-11	270
H4H2344S	5.79E+05	1.56E-06	2.69E-12	7409	1.01E+06	8.96E-05	8.91E-11	129
H4H2345S	5.16E+05	3.01E-05	5.84E-11	384	7.00E+05	7.44E-05	1.06E-10	155
H4H2346S	6.47E+05	1.44E-05	2.22E-11	803	1.75E+06	1.37E-04	7.81E-11	84
H4H2350P	5.09E+05	2.12E-05	4.16E-11	545	2.56E+06	1.26E-04	4.92E-11	92

(continued)

	25°C				37°C			
AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H4H2352S	2.14E+06	1.00E-06	4.67E-13	11550	2.28E+06	3.00E-05	1.32E-11	385
H4H2354S	5.80E+05	1.09E-05	1.89E-11	1056	1.02E+06	9.11E-05	8.95E-11	127
H4H2355S	6.11E+05	1.00E-06	1.64E-12	11550	1.10E+06	3.39E-05	3.10E-11	341
H4H2357S	7.79E+05	2.52E-05	3.24E-11	458	1.19E+06	9.40E-05	7.93E-11	123
H4H2364S	7.71 E+05	1.00E-06	1.30E-12	11550	1.26E+06	4.14E-05	3.28E-11	279
H1M2207N*	1.59E+05	2.60E-05	1.63E-10	444	2.03E+05	1.08E-04	5.31E-10	107
H2aM2210N*	1.68E+05	3.69E-05	2.20E-10	313	3.16E+05	7.66E-05	2.42E-10	151
H1M2212N*	1.12E+06	1.44E-05	1.28E-11	800	1.49E+06	6.17E-05	4.13E-11	187
H2aM2234N*	9.50E+05	9.60E-05	1.01E-10	120	1.26E+06	1.46E-04	1.16E-10	79
H1M2236N*	1.28E+06	1.76E-05	1.37E-11	658	1.58E+06	9.65E-05	6.10E-11	120
H1M2243N*	1.34E+05	1.00E-06	7.50E-12	11550	1.86E+05	2.18E-05	1.17E-10	529
*Tested for binding to hGFRα3-hFc, all other antibodies tested for binding to hGFRα3-mFc								

Example 4. Blocking of Human GFRa3 Binding to Human ARTEMIN by anti-GFRα3 Antibodies

[0183] The ability of anti-GFRα3 antibodies to block human GFRα3 binding to human ARTEMIN in the presence or absence of co-receptor human RET was determined using two different blocking ELISA formats.

[0184] In the first format, recombinant human ARTEMIN protein with a C-terminal myc-myc-hexahistidine tag (hARTEMIN-mmH; SEQ ID:369) was coated at 2 ug/ml in 96-well microtiter plates in PBS buffer overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount of human GFRα3 fused with a C-terminal human Fc tag (hGFRα3-hFc; SEQ ID:371) at 120 pM was pre-mixed with varying amounts of antibodies, ranging from 0 to -10 nM in serial dilutions, followed by an 1 hour incubation at room temperature (RT) to allow antibody-hGFRα3-hFc binding to reach equilibrium. The equilibrated sample solutions were then transferred to the hARTEMIN-mmH-coated plate. After 1 hour of binding, the plate was washed, then the bound hGFRα3-hFc was detected using HRP-conjugated anti-human IgG Fc specific antibody (Jackson Immunochemical, #109-035-098), and colorimetric signals were developed using a TMB HRP substrate (BD Biosciences, #51-2606KC and #51-2607KC). Absorbance was recorded at 450nm on a Victor X5 plate reader (Perkin Elmer) to determine the amount of free hGFRα3-hFc in the pre-equilibrated hGFRα3-hFc-antibody solutions that was able to bind to the plate coated with hARTEMIN-mmH. IC_{50} values, defined as the concentration of antibody required to reduce the signal from a constant concentration of hGFRα3-hFc by 50%, were calculated from the data using Prism software from GraphPad. The absorbance measured at the constant amount of 120pM hGFRα3-hFc in the absence of anti-GFRα3 antibody is defined as 0% blocking and the absorbance with no added hGFRα3-hFc is defined as 100% blocking. The observed absorbance in the wells containing the highest antibody concentration was used to calculate the maximum blocking percent shown in the table. The results are summarized in Table 6.

[0185] In the second ELISA format, the plates, samples and data were processed similarly as for the first format except both hARTEMIN-mmH and human RET with a C-terminal 10 histidine tag (hRET-10His; R&D Systems, # 1168-CR/CF) were coated for the blocking ELISA experiment. The 96-well microtiter plates were coated with a mixture of 1.2 ug/ml hARTEMIN-mmH and 6.9 ug/ml hRET-10His proteins in PBS overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount of biotinylated human GFRα3 with a C-terminal myc-myc-hexahistidine tag (biotin-hGFRα3-mmH; SEQ ID:370) at 1nM was pre-mixed with varied amounts of anti-GFRα3 antibodies, ranging from 0 to -100 nM in serial dilutions, followed by a 1 hour incubation at RT to allow antibody-biotin-hGFRα3-mmH binding to reach equilibrium. The equilibrated samples were then transferred to the coated plate. After 1 hour of binding, the plate was washed, then the bound biotin-hGFRα3-mmH was detected using HRP conjugated streptavidin (Pierce, #N200), and colorimetric signals were developed using TMB HRP substrates. IC_{50} values and the maximal blocking by each antibody are shown in the Table 6.

[0186] As shown in Table 6, 9 of the 23 anti-GFRα3 antibodies blocked 51-94% of the hGFRα3-hFc binding to coated hARTEMIN-mmH with IC_{50} values ranging from 43.8pM to 723pM in the first ELISA format. Eight of the 23 anti-GFRα3 antibodies caused the hGFRα3-hFc binding signal to increase ("enhancer" in Table 6) at many of the higher tested

antibody concentrations in the first ELISA format. Six of the 23 antibodies tested in the first ELISA format did not block or enhance the hGFRα3-hFc binding signal to coated hARTEMIN-mmH. As shown in Table 6, for the second ELISA format, 17 of the 23 anti-GFRα3 antibodies blocked 75-100% of the biotin-hGFRα3-mmH binding to dual-coated hARTEMIN-mmH and hRET-10His with IC_{50} values ranging from 403pM to 14.6nM. Also in the second ELISA format, five of the 23 anti-GFRα3 antibodies caused the biotin-hGFRα3-mmH binding signal to increase at lower antibody concentrations but blocked 28-95% of the biotin-hGFRα3-mmH binding to hARTEMIN-mmH and hRET-10His at antibody concentrations 1nM and above ("enhancer" in Table 6). One anti-GFRα3 antibody caused the biotin-hGFRα3-mmH binding signal to increase ("enhancer" in Table 6) at the higher tested antibody concentrations, with no blocking at any concentration, in the second ELISA format.

Table 6: ELISA Blocking of human GFRα3 to human ARTEMIN alone or human ARTEMIN and human RET

	ELISA format 1: Ab blocking 120pM hGFRα3-hFc binding to coated hARTEMIN-mmH		**ELISA format 2: Ab blocking 1nM biotin-hGFRa3-mmH binding to coated hARTEMIN-mmH and hRET-10His**	
AbPID	IC_{50} (M)	% max blocking	IC_{50} (M)	% max blocking
H4H2207N	enhancer	NB	7.30E-09	85
H4H2210N	enhancer	NB	enhancer	NB
H4H2212N	4.38E-11	81	4.03E-10	99
H4H2234N	8.29E-11	70	3.42E-09	97
H4H2236N3	enhancer	NB	enhancer	68
H4H2243N2	enhancer	NB	1.12E-09	95
H4H2291S	NB	NB	enhancer	28
H4H2292S	7.23E-10	89	1.76E-09	100
H4H2293P	2.60E-10	93	7.38E-09	95
H4H2294S	NB	NB	9.52E-10	95
H4H2295S	enhancer	NB	enhancer	44
H4H2296S	NB	NB	enhancer	91
H4H2341S	enhancer	NB	1.62E-09	98
H4H2342P	enhancer	NB	1.08E-09	97
H4H2344S	1.33E-10	94	4.59E-10	100
H4H2345S	enhancer	NB	1.46E-08	75
H4H2346S	9.78E-11	92	7.971E-10	99
H4H2350P	4.96E-10	93	1.29E-09	91
H4H2352S	6.58E-11	51	7.61E-10	100
H4H2354S	1.16E-10	92	1.32E-09	97
H4H2355S	NB	NB	enhancer	95
H4H2357S	NB	NB	3.28E-09	86
H4H2364S	NB	NB	1.45E-09	100
NB = non-blocker				

Example 5. Measuring the Ability of Anti-GFRa3 Antibodies to Block Activation of GFRa3 and RET by the Ligand ARTEMIN *in vitro*

[0187] The ability of anti-GFRα3 antibodies to block activation of GFRα3 and RET by its ligand ARTEMIN *in vitro* was determined using a cell-based assay. HEK293 cells modified to stably express both human GFRα3 (amino acids 1-400 of accession number NP_001487.2) and human RET (amino acids 1-1072 of accession number NP_065681) were

generated and then transduced with a SRE responsive luciferase reporter (SRE-luc; Sabiosciences, CCS-010L) (HEK293/hGFRα3/hRET cells).

[0188] Twenty thousand HEK293/hGFRα3/hRET/SRE-luc cells were seeded into Poly D-Lysine coated 96 well plates (Greiner, #35-4620) in Optimem (GIBCO, #31985) containing 0.5% FBS and then grown overnight in 5% CO_2 at 37°C. The cells were then incubated for 1 hour at room temperature with serial dilutions of anti-GFRα3 antibodies ranging from 5pM to 300nM. A constant dose (100pM) of human ARTEMIN expressed with a C-terminal myc myc hexahistidine tag (SEQ ID:369) was then added to the cells and incubated for an additional 6 hours. Luciferase activity was measured as relative light units (RLU) on a Victor luminometer (Perkin Elmer) after the addition of OneGlo reagent (Promega, #E6051). EC_{50} and IC_{50} values were calculated from a four-parameter logistic equation over a 12-point response curve using GraphPad Prism data analysis software.

[0189] Twenty-three anti-GFRα3 antibodies were tested for their ability to inhibit ARTEMIN-dependent activation of the HEK293/hGFRα3/hRET/SRE-luc cells. As shown in Table 7, all 23 antibodies tested blocked luciferase activity with IC_{50} values ranging from 0.2nM to 48.3nM, and 19 of 23 antibodies blocked to the baseline at a concentration of 300nM. Four of the 23 antibodies (H4H2344S, H4H2345S, H4H2346S, and H4H2354S-1) did not block to baseline at any of the antibody concentrations tested.

Table 7: Inhibition of ARTEMIN-dependent stimulation of HEK293/hGFRα3/hRET/ SRE-luc cells by anti-GFRα3 antibodies

AbPID	IC_{50} (nM)
H4H2294S	0.27
H4H2342P	1.0
H4H2212N	0.80
H4H2292S	4.6
H4H2243N2	0.30
H4H2352S	0.92
H4H2207N	2.4
H4H2210N	2.9
H4H2234N	2.3
H4H2236N3	1.5
H4H2291S	1.3
H4H2293P	20
H4H2294S	1.7
H4H2295S	1.5
H4H2296S	1.4
H4H2341S	7.1
H4H2344S	48
H4H2345S	26
H4H2346S	26
H4H2354S	22
H4H2355S	2.3
H4H2357S	4.9
H4H2364S	2.3

Example 6. Inhibition of ARTEMIN-sensitized capsaicin thermal hyperalgesia

[0190] To induce ARTEMIN-sensitized thermal hyperalgesia in mice, each mouse was pretreated with an intra-plantar injection of 0.5 micrograms mouse recombinant ARTEMIN (R&D Systems, #1085-AR) 24 hours before administering

an intra-plantar injection of 0.5 micrograms capsaicin (a sub-optimal dose) from a 100 mM solution in DMSO (Sigma-Aldrich, #M-2028). Thermal hyperalgesia was evaluated using the Hargreaves' Test, in which a beam of light is directed at the injected paw until the animal withdraws its paw. The latency to withdraw is recorded as a behavioral measure of nociception. Thermal hyperalgesia is consistently ARTEMIN-sensitized at 3 days after capsaicin administration based on significantly decreased paw withdrawal latencies. For these studies, a baseline value for withdrawal latency was measured before dosing with either ARTEMIN or capsaicin followed by a second measurement three days after capsaicin treatment. The experimenter conducting these assays was blind to the treatment group of the animals.

[0191] For all experiments evaluating the efficacy of human anti-GFRα3 antibodies in ARTEMIN-sensitized hyperalgesia, adult mice homozygous for the expression of human GFRα3 in place of mouse GFRα3 ("humanized GFRα3") were used. Both male and female mice were used in each assay, with sex balanced across treatment groups (a total of 8 mice per treatment or control group). Humanized GFRα3 mice were previously determined to have ARTEMIN-induced capsaicin thermal hyperalgesia latency responses similar to those observed in wild-type mice.

[0192] Six anti-GFRα3 antibodies (H4H2212N, H4H2243N2, H4H2292S, H4H2294S, H4H2342P, and H4H2352S-1) were tested in the model. All antibodies were diluted in phosphate-buffered saline (PBS) and were administered subcutaneously at 25mg/kg in a 1ml/100g body weight volume 24 hours prior to ARTEMIN injection into the hindpaw. In each experiment, one group of animals received an isotype control antibody.

[0193] Pain sensitivity for each treatment or control group was defined as percentage of baseline withdrawal latency (%BWL), calculated as the fractional change for each animal's time-based withdrawal latency (WL) three days after capsaicin treatment compared to their baseline withdrawal latency without capsaicin treatment:

$$\%BWL = [(WL_{(capsaicin)} - WL_{(no\ capsaicin)})/WL_{(no\ capsaicin)}] \times 100$$

[0194] Using %BWL, larger negative values indicate greater thermal hyperalgesia.

[0195] Table 8 shows the summary of group means (in boldface type) and standard error of the means (in italics) for percentage of baseline withdrawal latency (%BWL) in the ARTEMIN-sensitized capsaicin thermal hyperalgesia model assessed at three days after capsaicin injection.

[0196] As shown in Table 8, mice treated with anti-hGFRα3 antibodies exhibited increases in %BWL (smaller negative or positive values) compared to mice treated with the isotype control antibody. Four antibodies, H4H2352S, H4H2243N2, H4H2294S, and H4H2342P promoted the greatest resistance to thermal hyperalgesia across all experiments performed.

Table 8: Data Summary in the ARTEMIN-sensitized capsaicin thermal hyperalgesia model assessed at three days after capsaicin injection.

AbPID	%BWL			
	Exp. 323	**Exp. 361**	**Exp. 367**	**Exp. 380**
Isotype control	**-17** ± 7.6	**-32** ± *6.8*	**-40** ± *4.8*	**-35** ± *3.5*
H4H2292S	**0.72** ± *19*	***nd***	***nd***	**-26** ± *5.9*
H4H2352S	**27** ± *15*	***nd***	**-5.6** ± *9.4***	***nd***
H4H2243N2	**20** ± *18*	***nd***	***nd***	**21** ± *6.4****
H4H2294S	***nd***	**-9.0** ± *12*	**2.3** ± *12***	***nd***
H4H2342P	***nd***	**-12** ± *9.3*	**18** ± *8.3****	***nd***
H4H2212N	***nd***	**-22** ± *6.9*	***nd***	***nd***
significantly different than isotype control, **p<.01; ***p<.001 (nd=not tested in this experiment)				

Example 7. Testing of anti-GFRα3 Antibodies for Cross-Reactivity with GFRα1 and GFRα2

[0197] The ability of anti-GFRα3 antibodies to bind to GDNF-family receptors was assessed using an Octet Red biosensor (Fortebio, Inc.). Antibodies were tested for binding to either human GFRα1 expressed with a C-terminal human Fc tag and a hexahistidine tag (hGFRα1-hFc-6His, R&D Systems # 714-GR), human GFRα1 expressed with only a C-terminal human Fc tag (hGFRα1-hFc; SEQ ID: 376), human GFRα2 expressed with a C-terminal human Fc tag and a hexahistidine tag (hGFRα2-hFc-6His, R&D Systems #613-FR), human GFRα3 expressed with a C-terminal human Fc tag (hGFRα3-hFc, SEQ ID:371), or an irrelevant human Fc tagged protein. Antigens were captured onto anti-human Fc sensor tips from 10ug/mL solutions for 5 minutes. The coated sensor tips were then blocked with a 100ug/mL solution

of irrelevant human Fc antibodies for 5 minutes. Blocked sensor tips were then submerged into wells containing 667uM of each anti-GFRα3 antibody or buffer alone for 10 minutes. The experiment was performed at 25°C with a flow rate of 1000 rpm using HBST+BSA buffer (10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% w/v Surfactant P20, 0.1 mg/mL BSA, pH 7.4). The binding response (measured in units of nm) at each step of the experiment was monitored and recorded.

[0198] All six of the tested anti-GFRα3 antibodies showed binding above 1.0 nm to the hGFRα3-hFc protein, but did not demonstrate any measurable binding to the other GDNF-family receptors or to the irrelevant human Fc tagged protein, as shown in Table 9.

Table 9. Reactivity of Anti-GFRα3 Antibodies with GFRα1, GFRα2 and GFRα3

Antigen	Capture Level (nm) +/- Std dev	100 ug/mL H4H2294S Bound (nm)	100 ug/mL H4H2342P Bound (nm)	100 ug/mL H4H2243N2 Bound (nm)	100 ug/mL H4H2212N Bound (nm)	100 ug/mL H4H2352S Bound (nm)	100 ug/mL H4H2292S Bound (nm)	Buffer
hGFRα1-hFc	1.89 ± 0.14	0.04	0.06	0.03	0.00	0.02	0.05	-0.07
hGFRα1-hFc-6his	1.66 ± 0.10	0.03	0.08	0.03	-0.01	0.03	0.03	-0.07
hGFRα2-hFc-6his	1.49 ± 0.09	0.06	0.12	0.06	0.02	0.04	0.05	-0.06
hGFRα3-hFc	1.68 ± 0.10	1.17	1.59	1.11	1.18	1.25	1.04	-0.09
Irrelevant hFc tagged protein	1.00 ± 0.06	0.03	0.07	0.03	0.00	0.03	0.02	-0.08

Example 8. Measuring the Ability of Anti-GFRa3 antibodies to block ARTEMIN stimulation in a HEK293/MfGFRa3/MfRet/SRE-Luc bioassay

[0199] The ability of anti-GFRα3 antibodies to block activation of cynomolgus GFRα3 and cynomolgus RET by its ligand ARTEMIN *in vitro* was determined using a cell-based assay. HEK293 cells modified to stably express both cynomolgus GFRα3 (MfGFRα3; SEQ ID: 377) and cynomolgus RET (MfRET; SEQ ID: 378) were generated and then transduced with a Cignal Lenti SRE Reporter (SA Biosciences, #CLS-010L) expressing the firefly luciferase gene under the control of a minimal CMV promoter and tandem repeats of the serum response element to generate the HEK293/MfGFRα3/MfRet/SRE-Luc cell line.

[0200] For the bioassay, 20,000 HEK293/MfGFRα3/MfRet/SRE-Luc cells were seeded onto Poly D-Lysine coated 96 well plates (Greiner, #35-4620) in Optimem (GIBCO, #31985) containing 0.5% FBS and then grown overnight at 5% CO_2 at 37°C. The cells were then incubated for 1 hour with serial dilutions of anti-GFRα3 antibodies ranging from 5pM to 300nM. A constant dose (500pM) of human ARTEMIN expressed with a C-terminal myc-myc-hexahistidine tag (Human ARTEMIN-MMH; SEQ ID: 369) was then added to the cells and incubated for an additional 6 hours. To determine the EC_{50} value of human ARTEMIN-MMH from dose response curves, serial dilutions of human ARTEMIN-MMH ranging from 0.5 pM to 10nM was added to the cells without antibodies and incubated for 6 hours at 37°C. Luciferase activity was measured as relative light units (RLU) on a Victor luminometer (Perkin Elmer) after the addition of OneGlo reagent (Promega, #E6051). EC_{50} and IC_{50} values were calculated from a four-parameter logistic equation over a 12-point response curve using GraphPad Prism data analysis software.

[0201] Six anti-GFRα3 antibodies were tested for their ability to inhibit ARTEMIN-dependent activation of the HEK293/MfGFRα3/MfRET/SRE-luc cells. As shown in Table 10, all six antibodies tested completely blocked luciferase activity with IC_{50} values ranging from 0.7nM to 2.5nM. Human ARTEMIN-MMH stimulated SRE-dependent luciferase activity in the HEK293/mfGFRα3/mfRet/SRE-LUC cell line with an EC_{50} value of 70pM.

Table 10: Inhibition of ARTEMIN-dependent stimulation of HEK293/MfGFRa3/MfRET/ SRE-luc cells by anti-GFRa3 antibodies

Antibody	IC_{50} (nM)
H4H2294S	0.7
H4H2342P	2.5
H4H2212N	1.8
H4H2292S	1.5
H4H2243N2	0.8
H4H2352S	1.3

Example 9. Generation of a Bi-specific Anti-GFRa3 Antibody

[0202] Various bi-specific antibodies are generated for use in practicing the methods of the invention. For example, GFRα3-specific antibodies are generated in a bi-specific format (a "bi-specific") in which variable regions binding to distinct epitopes on GFRα3 are linked together to confer dual-epitope specificity within a single binding molecule. Appropriately designed bi-specifics may enhance overall GFRα3 blocking efficacy through increasing both GFRα3 specificity and binding avidity. Variable regions with specificity for individual different epitopes within any of the three cysteine repeats or that can bind to different regions within one epitope of any of the three cysteine repeats are paired on a structural scaffold that allows each variable region to bind simultaneously to the separate epitopes, or to different regions within one epitope. In one example for a bi-specific, heavy chain variable regions (V_H) from a binder with specificity for one epitope within one cysteine repeat are recombined with light chain variable regions (V_L) from a series of binders having specificity for a second epitope within any of the other two cysteine repeats to identify non-cognate V_L partners that can be paired with an original V_H without disrupting the original specificity for that V_H. In this way, a single V_L segment *(e.g.,* V_L1) can be combined with two different V_H domains (*e.g.,* V_H1 and V_H2) to generate a bi-specific comprised of two binding "arms" (V_H1- V_L1 and V_H2- V_L1). Use of a single V_L segment reduces the complexity of the system and thereby simplifies and increases efficiency in cloning, expression, and purification processes used to generate the bi-specific (See, for example, USSN13/022759 and US2010/0331527).

[0203] Alternatively, antibodies that bind both GFRα3 and a second target, such as, but not limited to, for example, RET may be prepared in a bi-specific format using techniques described herein, or other techniques known to those skilled in the art. Antibody variable regions binding to distinct GFRα3 regions that are extracellularly exposed are linked together with variable regions that bind to relevant sites on, for example, the ligand, artemin, other GFRα receptors, or to RET, to confer dual-antigen specificity within a single binding molecule. Variable regions with specificity for individual epitopes of GFRα3, are combined with a variable region with specificity for, for example, artemin and are paired on a structural scaffold that allows each variable region to bind to the separate antigens.

[0204] The bi-specific binders are tested for binding and functional blocking of the target antigens, for example, GFRα3 and/or artemin, other GFRα receptors, or RET, in any of the assays described above for antibodies. For example, standard methods to measure soluble protein binding are used to assess the bispecific interaction with its antigen(s), such as Biacore, ELISA, size exclusion chromatography, multi-angle laser light scattering, direct scanning calorimetry, and other methods. Binding of bi-specific antibodies to cells expressing GFRα3 is determined through flow cytometry using a fluorescently labeled secondary antibody recognizing the target antigen on the cells. Binding experiments with peptides can also be conducted using surface plasmon resonance experiments, in which real-time binding interaction of peptide to antibody is measured by flowing a peptide or bi-specific across a sensor surface on which bi-specific or peptide, respectively, is captured. Functional *in vitro* blocking of the GFRα3 receptor by a bi-specific is determined using any bioassay such as that described herein, or by *in vivo* determination of reaction to pain in appropriate animal models, such as those described herein. Functional *in vitro* blocking of GFRα3 or its ligand, artemin, by a bi-specific is determined using any bioassay such as that described in WO2010/077854, or in US2010/0166768, or by *in vivo* determination of hypersensitivity to thermal stimuli in appropriate animal models, such as those described herein.

Example 10. Surface plasmon resonance derived binding affinities and kinetic constants of monoclonal anti-mouse GFRα3 antibodies

[0205] Binding associative and dissociative rate constants (k_a and k_d, respectively) and calculated equilibrium dissociation constants and dissociative half-lives (K_D and $t_{1/2}$, respectively) for antigen binding to anti-mouse GFRα3 antibodies were determined using a real-time surface plasmon resonance biosensor (Biacore 3000) assay at 25°C. Antibodies

were tested for binding to mouse GFRα3 expressed with myc-myc-hexahistidine tag (mGFRα3-MMH; SEQ ID: 379,). Anti-mouse GFRα3 antibodies were captured on a goat anti-mouse IgG polyclonal antibody (GE Healthcare, # BR-1008-38) surface created through direct amine coupling to a Biacore CM5 sensor chip. Kinetic experiments were carried out using HBS-EP

[0206] (10mM HEPES, 150mM NaCl, 3mM EDTA, 0.05% Surfactant P20, at pH 7.4) as both the running buffer and the sample buffer. Binding to mouse GFRα3-MMH was evaluated by injecting several concentrations ranging from 100nM to 6.25 nM (2-fold dilutions) across the captured antibody surface. Antibody-antigen association was monitored for up to 5 minutes, while dissociation in buffer was monitored for up to 10 minutes. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0c curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives ($t_{1/2}$) were calculated from the kinetic rate constants as: K_D (M) = k_d / k_a and $t_{½}$ (min) = [ln2/(60*k_d)].

[0207] As shown in Table 11, the two anti-mouse GFRα3 antibodies tested, M1M6986N and M1M6977N, bound to mGFRα3-MMH at 25°C with K_D values of 23.1pM and 107pM, respectively.

Table 11: Kinetics of mGFRα3-MMH binding to different anti-mouse GFRα3 antibodies at 25°C

AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
M1M6986N	1.02E+06	2.35E-05	2.31E-11	491
M1M6977N	3.84E+05	4.1E-05	1.07E-10	282

Example 11. Mouse GFRa3 Blocking ELISA

[0208] The ability of anti-mouse GFRα3 antibodies to block mouse GFRα3 binding to mouse ARTEMIN in the presence or absence of co-receptor mouse RET was determined using two different blocking ELISA formats. In the first format, recombinant mouse ARTEMIN (R&D cat# 1085-AR/CF) protein was coated at 2ug/mL (166nM) in 96-well microtiter plates in PBS buffer overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount (3.5nM) of biotinylated mouse GFRα3 with a C-terminal myc-myc-hexahistidine tag (Biotin- mGFR□3-MMH, SEQ ID:379) was pre-mixed with varying amounts of antibodies, ranging from 100nM to 1.6 pM in serial dilutions, followed by 1 hour incubation at room temperature (RT) to allow antibody-biotin-mGFRα3-MMH binding to reach equilibrium. The equilibrated sample solutions were then transferred to the mARTEMIN-coated plate. After 1 hour of binding, the plate was washed, then the bound biotin-mGFRα3-MMH was detected using Streptavidin-HRP (Pierce, #N200) and colorimetric signals were developed using a TMB HRP substrate (BD Biosciences, #51-2606KC and #51-2607KC). Absorbance was recorded at 450nm on a Victor X5 plate reader (Perkin Elmer) to determine the amount of free biotin-mGFRα3-MMH in the pre-equilibrated biotin-mGFRα3-MMH-antibody solutions that was able to bind to the plate-coated mARTEMIN. IC_{50} values, defined as the concentration of antibody required to reduce the signal from a constant concentration of biotin-mGFRα3-MMH by 50%, were calculated from the data using Prism software from GraphPad. The absorbance measured at the constant amount of biotin-mGFRα3-MMH in the absence of anti-mouse GFRα3 antibody is defined as 0% blocking and the absorbance with no added biotin-mGFRα3-MMH is defined as 100% blocking. The observed absorbance in the wells containing the highest antibody concentration was used to calculate the maximum blocking percent shown in the table. The results are summarized in Table 12.

[0209] In the second ELISA format, the plates, samples and data were processed similarly as for the first format except both mouse RET expressed with C-terminal hFc and hexahistidine tags (mRET-hFc-6His; R&D cat# 482-RT/CF) and mARTEMIN (R&D cat# 1085-AR/CF) were coated for the blocking ELISA experiment. The 96-well microtiter plates were coated with a mixture of 1.2ug/mL (100nM) mARTEMIN and 9.5ug/mL (100nM) mRET-hFc-6His proteins in PBS overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount (350pM) of biotin-mGFRα3-MMH was pre-mixed with varied amounts of anti-mouse GFRα3 antibodies, ranging from 100nM to 1.6pM in serial dilutions, followed by a 1 hour incubation at RT to allow antibody- biotin-mGFRα3-MMH binding to reach equilibrium. The equilibrated samples were then transferred to the coated plate. After 1 hour of binding, the plate was washed, then the bound biotin-mGFRα3-MMH was detected using HRP conjugated streptavidin and colorimetric signals were developed using TMB HRP substrates. IC_{50} values and the maximal blocking by each antibody are shown in the Table 12.

[0210] As shown in Table 12, only one anti-mouse GFRα3 antibody tested, M1M6986N, demonstrated the ability to block biotin-mGFRα3-MMH from binding to the coated mARTEMIN plate with an IC_{50} value of 69.1pM. The other anti-mouse GFRα3 antibody tested, M1M6977N, did not demonstrate any measurable blockade in this ELISA format. Both anti-mouse GFRα3 antibodies tested, M1M6986N and M1M6977N, demonstrated the ability to completely block biotin-mGFRα3-MMH from binding to the plates coated with both mARTEMIN and mRET-hFc-6His, with IC_{50} values of 47.2pM and 366pM, respectively.

Table 12: ELISA Blocking of mouse GFRα3 to mouse ARTEMIN alone or mouse ARTEMIN and mouse RET

	ELISA format 1: Antibody blocking 3.5nM biotin- mGFRα3-MMH binding to coated mARTEMIN		ELISA format 2: Antibody blocking 350pM biotin- mGFRα3-MMH binding to coated mARTEMIN and mRET-hFc-6His	
AbPID	IC_{50} (M)	% max blocking	IC_{50} (M)	% max blocking
M1M6986N	6.91E-11	100%	4.72E-11	100%
M1M6977N	NB		3.66E-10	100%
NB = non-blocker				

Example 12. Cell based Luciferase bioassay

[0211] The ability of anti-mouse GFRα3 antibodies to block activation of mouse GFRα3 and mouse RET by its ligand mouse ARTEMIN *in vitro* was determined using a cell-based assay. HEK293 cells modified to stably express both mouse GFRα3 (amino acids 1-397 of accession number AAH66202.1) and mouse RET (amino acids 1-1115 of accession number NP_033076.2) were generated and then transduced with a SRE responsive luciferase reporter (SRE-luc; Sabiosciences, CCS-010L) (293/mGFRα3/mRET/SRE-luc cells).

[0212] Twenty thousand 293/mGFRα3/mRET/SRE-luc cells were seeded into Poly D-Lysine coated 96 well plates (Greiner, #35-4620) in Optimem (GIBCO, #31985) containing 0.5% FBS and then grown overnight in 5% CO_2 at 37°C. The cells were then incubated for 1 hour at room temperature with serial dilutions of anti-mouse GFRα3 antibodies ranging from 3 nM to 44 nM. A constant dose (100 pM) of mouse ARTEMIN (R&D, # 1085-AR/CF) was then added to the cells and incubated for an additional 6 hours. Luciferase activity was measured as relative light units (RLU) on a Victor luminometer (Perkin Elmer) after the addition of OneGlo reagent (Promega, #E6051). EC_{50} and IC_{50} values were calculated from a four-parameter logistic equation over a 12-point response curve using GraphPad Prism data analysis software.

[0213] As shown in Table 13, both anti-mouse GFRα3 antibodies tested, M1M6986N and M1M6977N demonstrated the ability to inhibit mouse ARTEMIN-dependent stimulation of 293/mGFRα3/mRET/SRE-luc cells with IC_{50} values of approximately 44nM and 3nM, respectively.

Table 13: Inhibition of ARTEMIN-dependent stimulation of 293/mGFRα3/mRET/SRE-luc cells by anti-mouse GFRα3 antibodies

Antibody	IC_{50} (nM)
M1M6986N	44 ± 3 (n=2)
M1M6977N	3 ± 1 (n=3)

Examples 13, 14 and 15: The effect of anti-mouse GFRa3 antibodies in animal models of bone cancer pain and osteoarthritic pain

[0214] The antibodies described herein are high affinity human antibodies to the GPI-linked alpha receptor for artemin, GFRα3. Since these antibodies to human GFRα3 do not cross-react with mouse GFRα3, *in vivo* assays with these antibodies can only be conducted in mice genetically altered to replace the mouse GFRα3 sequence with that of human GFRα3. Initial *in vivo* experiments in these $GFR\alpha3^{hu/hu}$ mice using pharmacological inhibition of artemin-sensitized capsaicin revealed efficacy of four human antibodies in this *in vivo* assay. In order to expedite the generation of efficacy data, mouse GFRα3 antibodies were generated to serve as surrogates to the human antibodies. Mice of a mixed C57BL6/129Sv strain that were homozygous for deletion of the endogenous GFRα3 gene were immunized with recombinant mouse GFRα3 extracellular domain expressed in Chinese hamster ovary cells. A specific immune response to GFRα3 was confirmed by immunoassays of serum from the immunized mice. Spleens were collected from mice exhibiting a high specific immune response, and antibody-producing hybridoma cells were generated by fusion of the isolated splenocytes with mouse myeloma cells following standard hybridoma procedures. Hybridoma supernatants were further screened in immunoassays for binding to GFRα3 and for their ability to block binding of GFRα3 to either artemin or artemin/Ret coated on a solid surface in an immunoassay format. Supernatants were also screened for their ability to block artemin stimulation of the GFRα3/Ret co-receptor pathway in a cell-based bioassay. Variable-region antibody sequences were obtained by PCR amplification of selected hybridoma clones whose antibody proteins exhibited potent

blocking in the cell-based assay, and these sequences were used to produce full-length recombinant anti-mouse GFRα3 antibodies with a mouse IgG1 isotype. Two antibodies were selected for *in vivo* testing that potently inhibited artemin signaling in the cell-based assay. In the *in vitro* binding immunoassay, antibody M1M6986N blocked binding of GFRα3 to both artemin or artemin/Ret coated on a solid surface and is referred to here as a direct blocker. Antibody M1M6977N blocked binding of GFRα3 to coated artemin/Ret but not to artemin alone in the *in vitro* immunoassay and is referred to here as an indirect blocker. These two mouse antibodies, M1M6986N and M1M6977N, were selected for testing in the artemin-sensitized capsaicin thermal analgesia model (described in Example 6), since these two antibodies demonstrated similar binding and blocking profiles to the efficacious human antibodies. These two antibodies were screened for their ability to block artemin-induced sensitization of hyperalgesia *in vivo* in wild type mice. Like their human antibody counterparts, both antibodies significantly inhibited artemin's sensitizing effect on capsaicin thermal hyperalgesia three days after capsaicin injection (Figure 1).

Example 13: Fibrosarcoma Model of Bone Cancer Pain

Methodology

Subjects

[0215] Adult male mice on a C57Bl6 background strain were used for two fibrosarcoma experiments at approximately 12 weeks of age. The experimenters measuring outcome data for this experiment were blind to treatment group of the animals throughout data collection, compilation, and analysis.

Bone Cancer Model

[0216] To induce bone cancer pain, the mice were anesthetized and then injected intrafemorally with $1.0x10^6$ MC57G fibrosarcoma cells. These cells are derived from a C57Bl/6 mouse fibrosarcoma tumor line. Tumors typically grow aggressively in this model, such that bone destruction is evident by 14 days after tumor implantation. Radiographs were taken at days 7, and 10, and 14 after implantation to verify tumor growth and bone destruction. Bone destruction was scored on a three-point scale such that 0 represented no destruction and 3 represented complete destruction of the femur in the region of the tumor.

Antibody Treatment

[0217] Each animal received 30mg/kg s.c. antibody injections administered the day before cancer cell implantation and again on day 7. Animals were pseudo-randomly assigned to one of two or three treatment groups: 1) M2M180N isotype (negative) control antibody in two separate experiments, 2) M1M6977N anti-mouse GFRα3 antibody in two separate experiments or 3) M1M6986N anti-mouse GFRα3 antibody in the second experiment only. M1M6986 blocks artemin's interaction with GFRα3, and is thereby considered a "direct" blocker of artemin's action. In contrast, M1M6977N inhibits artemin's action through the GFRα3/RET complex, and is therefore considered an "indirect" inhibitor.

Measures of Nociception

[0218] Nociceptive responses to the bone tumor were measured using the von Frey Hair test for evoked mechanical (tactile) allodynia, the dynamic weight bearing (DWB) test for willingness to bear weight on a limb, and guarding behavior. Von Frey test results are expressed as grams of pressure required for paw withdrawal. Weight bearing results are expressed as percent body weight placed on the ipsilateral limb. Guarding behavior is expressed as time spent guarding the limb over a two-minute period.

Results

Bone Destruction

[0219] There was no significant effect of antibody treatment on bone destruction score in either experiment suggesting that the antibody treatment had no impact on the severity of the bone cancer itself (data not shown).

Nociceptive Behavior

[0220] There was a statistically significant decrease in tactile allodynia with GFRα3 antibody treatment after fibrosa-

rcoma injection in the first experiment (F(1,20)=9.189, p=.007, Figure 2A) and a statistical trend toward efficacy overall in the second experiment (F(2,29)=3.069, p<.062, Figure 2B), with individual comparisons sometimes achieving significance in the second study (Figure 2B).

[0221] There was no statistically significant effect of GFRα3 antibodies on dynamic weight bearing on the ipsilateral limb measured 14 days after implantation of bone with fibrosarcoma cells in either experiment, although the first experiment revealed a statistical trend toward efficacy with M1M6977N treatment (t(10)=2.047, p=.068, Figure 3A; F(2,28)=1.598, p=.220, Figure 3B).

[0222] GFRα3 antibodies significantly reduced limb guarding after bone cancer implantation in both fibrosarcoma experiments (F(1,20)=12.270, p=.002, Figure 4A; F(2,29)=3.576, p=.041, Figure 4B).

Conclusion

[0223] Treatment with anti-mouse GFRα3 antibodies significantly reduced nociceptive behaviors in this bone cancer pain model as measured by evaluation of guarding and the von Frey Test of tactile allodynia. In addition, there was a statistical trend toward efficacy of the M1M6977N antibody in weight bearing differential in one experiment. Bone destruction scores were not different in groups receiving anti-mouse GFRα3 antibodies, suggesting that differences in pain-related measures could not be accounted for by differences in cancer severity. Therefore, our data suggest that neutralizing antibodies against GFRα3 could be efficacious against bone cancer pain. Because sarcoma cells are more often primary tumors than metastases in bone, and because most bone cancers derive from metastases of primary tumors from other sites, these antibodies were also tested in a model of breast (mammary) carcinoma-induced bone cancer pain. Breast and prostate tumors are among the most common tumors found to metastasize to bone.

Example 14: Breast Carcinoma Model of Bone Cancer Pain

Methodology

Subjects

[0224] Adult male mice on a Balb/c background strain were used for a mammary carcinoma bone cancer experiment at approximately 12 weeks of age. The experimenters measuring outcome data for this experiment were blind to treatment group of the animals throughout data collection, compilation, and analysis.

Bone Cancer Model

[0225] To induce bone cancer pain, the mice were anesthetized and then injected intrafemorally with 10,000 4T-1 mammary carcinoma cells. These cells are derived from a Balb/c mammary carcinoma tumor line. Tumors typically grow aggressively in this model, such that tumors are severe by 18 days after implantation. Radiographs were taken at days 10, 14, and 19 after implantation to verify tumor growth and bone destruction. Bone destruction was scored on a three-point scale such that 0 represented no destruction and 3 represented complete destruction of the femur in the region of the tumor.

Antibody Treatment

[0226] Each animal received 30mg/kg s.c. antibody injections administered the day before cancer cell implantation and two times per week thereafter. Animals were pseudo-randomly assigned to one of three treatment groups: 1) M2M180N isotype (negative) control antibody, 2) M1M6977N anti-mouse GFRα3 antibody, or 3) M1M6986N anti-mouse GFRα3 antibody. M1M6986N blocks artemin's interaction with GFRα3, and is thereby considered a "direct" blocker of artemin's action. In contrast, M1M6977N inhibits artemin's action through the GFRα3/RET complex, and is therefore considered an "indirect" inhibitor.

Measures of Nociception

[0227] Nociceptive responses to the bone tumor were measured using the von Frey Hair test for evoked mechanical (tactile) allodynia, the dynamic weight bearing (DWB) test for willingness to bear weight on a limb, and guarding behavior. Von Frey test results are expressed as grams of pressure required for paw withdrawal. Weight bearing results are expressed as percent body weight placed on the ipsilateral limb. Guarding behavior is expressed as time spent guarding the limb over a two-minute period.

Results

Bone Destruction

[0228] There was no significant effect of antibody treatment on bone destruction score in this model, suggesting that the antibody treatment had no impact on the severity of the bone cancer itself.

Nociceptive Behavior

[0229] There was a statistically significant decrease in tactile allodynia with GFRα3 antibody treatment after carcinoma ($F(2, 25)=8.626$, $p=.001$, Figure 5).

[0230] There were no statistically significant overall effects of GFRα3 antibodies on dynamic weight bearing on the ipsilateral limb, although the overall effect of treatment achieved a statistical trend and M1M6977N achieved significant efficacy on post hoc comparison at 11 days (A), but not 18 days (B), after implantation of bone with carcinoma cells (11 day $F(2,25)=2.939$, $p=.071$, Figure 6A; 18 day $F(2,25)=0.149$, $p=.862$, Figure 6B).

[0231] GFRα3 antibodies significantly reduced limb guarding after bone cancer implantation in this model ($F(2,25)=4.222$, $p=.026$, Figure 7).

Conclusion

[0232] Treatment with anti-mouse GFRα3 antibodies significantly reduced nociceptive behaviors in this bone cancer pain model as measured by evaluation of guarding and the von Frey Test of tactile allodynia. In addition, there was evidence of efficacy of the REGN1967 antibody in weight bearing differential at one time point. Bone destruction scores were not different in groups receiving anti-mouse GFRα3 antibodies, suggesting that differences in pain-related measures could not be accounted for by differences in cancer severity. Therefore, our data suggest that neutralizing antibodies against GFRα3 could be efficacious against bone cancer pain in this model of metastatic bone cancer pain.

Example 15. Destabilization of the Medial Meniscus (DMM) Model of Osteoarthritic Pain Methodology

Subjects

[0233] Adult male mice on a C57Bl6 background strain were used for the DMM experiment starting at approximately 12 weeks of age. The experimenters measuring outcome data for this experiment were blind to treatment group of the animals throughout data collection, compilation, and analysis.

DMM Model

[0234] In the DMM model, the medial meniscus of one knee is destabilized and the animal is allowed to develop disease for 16 weeks. During the 16 week period, animals develop tactile allodynia and increases in bone volume and bone mineral content in the injured knee resembling early human osteoarthritis. Tactile allodynia was verified in animals by von Frey Test at 16 weeks before the initiation of antibody treatment.

Antibody Treatment

[0235] Each animal received 30mg/kg s.c. antibody injections administered weekly starting 16 weeks after DMM surgery. Animals were pseudo-randomly assigned to one of three treatment groups: 1) M2M180N isotype (negative) control antibody, 2) M1M6977N anti-mouse GFRα3 antibody, or 3) M1M6986N anti-mouse GFRα3 antibody. M1M6986N blocks artemin's interaction with GFRα3, and is thereby considered a "direct" blocker of artemin's action. In contrast, M1M6977N inhibits artemin's action through the GFRα3/RET complex, and is therefore considered an "indirect" inhibitor.

Measures of Nociception

[0236] Nociceptive responses to the knee pathology were measured using the von Frey Hair test for evoked mechanical (tactile) allodynia.

Results

Nociceptive Behavior

[0237] There was a statistically significant decrease in tactile allodynia with GFRα3 antibody treatment after DMM ($F(2, 27)=21.68$, $p=.0001$, Figure 8).

Conclusion

[0238] Treatment with mouse GFRα3 antibodies had a statistically significant effect on tactile allodynia such that the groups treated with the two GFRα3 antibodies consistently showed less allodynia than the isotype control starting 14 days after the initiation of weekly treatment. These data suggest the possibility that GFRα3 antibodies will be efficacious against chronic human osteoarthritic pain.

Example 16. Cross-Competition Analysis of anti-GFRa3 Antibodies

[0239] A cross-competition assay was conducted to assess the ability of select antibodies to compete with one another for binding to human GFRα3 using an Octet RED384 biosensor (Fortebio Inc.). The entire experiment was performed at 25°C with the flow rate of 1000rpm in Octet HBST buffer (0.01 M HEPES pH7.4, 0.15M NaCl, 3 mM EDTA, 0.05% v/v Surfactant P20, 0.1mg/mL BSA). To assess whether 2 antibodies were able to compete with one another for binding to their respective epitopes on biotinylated recombinant human GFRα3 expressed with a C-terminal myc-myc-hexahistidine tag (biotin-hGFRα3-mmH; SEQ ID:370), around ~1.2nm of biotin-hGFRα3-mmH was first captured onto streptavidin-coated Octet sensor tips (Fortebio Inc, # 18-5019) by submerging the tips for 1 minute into a 10μg/mL solution of biotin-hGFRα3-mmH. The antigen coated sensor tips were then placed into wells containing 25μg/mL solution of a first anti-GFRα3 monoclonal antibody for 4 minutes to saturate the biotin-hGFRα3-mmH surface. The sensor tips were then subsequently dipped into wells containing 25μg/mL solution of a second anti-GFRα3 monoclonal antibody. The sensor tips were washed in Octet HBST buffer in between every step of the experiment. The real-time binding response was monitored during the course of the experiment and the binding response at the end of every step was recorded as shown in Figure 9. The response of mAb-2 binding to biotin-hGFRα3-mmH pre-complexed with the first antibody was compared and competitive/non-competitive behavior of different anti-GFRα3 monoclonal antibodies was determined.

[0240] As shown in Figure 9, dark grey boxes with black font represent binding response for self-competition. Antibodies competing in both directions, independent of the order of binding are represented with black boxes and white font. No competition between antibodies that suggest distinct binding epitope is represented as white box with black font.

[0241] Nine antibodies (H4H2236N3, H4H2342P, H4H2295S, H4H2294S, H4H2291S, H4H2357S, H4H2355S, H4H2296S, and H4H2243N2) bi-directionally compete with each other for binding to biotin-hGFRα3-mmH. Eight of the 9 (H4H2236N3, H4H2342P, H4H2295S, H4H2294S, H4H2291S, H4H2357S, H4H2355S, and H4H2296S) do not compete with any other anti-GFRα3 antibody tested, while H4H2243N2 also bi-directionally competes with two additional anti-GFRα3 antibodies tested (H4H2212N and H4H2352S). H4H2212N and H4H2352S bi-directionally compete with each other and H4H2243N2 for binding to biotin-hGFRα3-mmH, but while H4H2212N does not compete with any other anti-GFRα3 antibodies tested, H4H2352S also bi-directionally competes with an additional anti-GFRα3 antibody tested (H4H2292S). One anti-GFRα3 antibody tested, H4H2350P, does not compete with any of the anti-GFRα3 antibodies tested for binding to biotin-hGFRα3-mmH.

[0242] Aspects of the Invention:

1. An isolated monoclonal antibody or an antigen-binding fragment thereof that specifically binds to GFRα3, having one or more of the following characteristics:

(i) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance;
(ii) demonstrates the ability to block about 50-100% of the binding of GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM;
(iii) demonstrates the ability to block about 20% to about 100% of the binding of GFRα3 to a solid support coated with a mixture of artemin and RET;
(iv) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM;
(v) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain;
(vi) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo;*
(vii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis;
(viii) does not cross-react with other GFR co-receptors for RET;
(ix) comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group

consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226,242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; or
(x) comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

2. The isolated monoclonal antibody or an antigen-binding fragment thereof of aspect 1, wherein the antibody is selected from the group consisting of a murine antibody, a chimeric antibody, a humanized antibody and a human antibody.

3. The isolated monoclonal antibody or an antigen-binding fragment thereof of either aspects 1 or 2, wherein the antibody does not cross-react with human GFRα1 or human GFRα2

4. The isolated monoclonal antibody or an antigen-binding fragment thereof of any one of aspects 1-3, wherein the antibody is a human monoclonal antibody comprising (a) a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397 and (b) a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

5. The isolated monoclonal antibody or an antigen-binding fragment thereof of any one of aspects 1-4, wherein the antibody demonstrates the ability to block about 50-95% of the binding of human GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 750 pM.

6. The isolated monoclonal antibody or an antigen-binding fragment thereof of any of aspects 1-4, wherein the antibody or the antigen-binding fragment thereof blocks about 75-100% of the binding of human GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 400 pM to about 15 nM.

7. The isolated monoclonal antibody or an antigen-binding fragment thereof of any one of aspects 1-4, wherein the antibody or the antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of human RET with an IC_{50} ranging from about 300 pM to about 5 nM.

8. The isolated monoclonal antibody or an antigen-binding fragment thereof of any one of aspects 1-4, wherein the antibody or the antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of cynomolgus RET with an IC_{50} ranging from about 0.7 nM to about 2.5 nM.

9. An isolated antibody or antigen-binding fragment thereof that binds specifically to human GFRα3, wherein the antibody comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

10. The isolated antibody or antigen-binding fragment thereof of aspect 9, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397.

11. The isolated antibody or antigen-binding fragment thereof of either aspect 9 or 10, wherein the antibody or antigen-binding fragment comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

12. The isolated antibody or antigen-binding fragment of any one of aspects 9-11, comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 381/389 and 397/405.

13. The isolated antibody or antigen-binding fragment of aspect 12, comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NO: 50/58, 146/154, 210/218 and 290/298.

14. The isolated antibody or antigen-binding fragment of any one of aspects 9-12, comprising:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 383 and 399;
(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 385 and 401;
(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 387 and 403;
(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 391 and 407;
(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 393 and 409; and
(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 395 and 411.

15. An isolated antibody or antigen-binding fragment thereof that competes for specific binding to human GFRα3 with an antibody or antigen-binding fragment comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362, 381/389 and 397/405.

16. An isolated antibody or antigen-binding fragment thereof that binds the same epitope on human GFRα3 that is recognized by an antibody comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362, 381/389 and 397/405.

17. An isolated nucleic acid molecule encoding the antibody or antigen-binding fragment of any of aspects 9-14.

18. An expression vector comprising the nucleic acid molecule of aspect 17.

19. A method of producing an anti-GFRα3 antibody or antigen-binding fragment thereof comprising the steps of introducing the expression vector of aspect 18 into an isolated host cell, growing the cell under conditions permitting production of the antibody or fragment thereof, and recovering the antibody so produced.

20. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any one of aspects 1 through 16 and a pharmaceutically acceptable carrier or diluent.

21. A method for treating a GFRα3-related condition or disease, or the pain associated with the GFRα3-related condition or disease, the method comprising administering the antibody or antigen-binding fragment of any of aspects 1-16, to a patient in need thereof, wherein the GFRα3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

22. The method of aspect 21, wherein the GFRα3-related condition or disease is selected from the group consisting of acute pain, chronic pain, neuropathic pain, inflammatory pain, a functional pain syndrome, arthritis, pancreatitis, osteoarthritis, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, neurodegenerative disorders, movement disorders, neuroendocrine disorders, ataxia, visceral pain, gout, post-herpetic neuralgia, diabetic neuropathy, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, post-surgical

pain, hereditary erythromelalgia, dental pain, rhinitis, cancer pain, complex regional pain syndrome (CRPS), inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and bladder disorders.

23. The method of aspect 22, wherein the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome.

24. The method of aspect 22, wherein the cancer pain is associated with a cancer selected from the group consisting of endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, non-small cell lung cancer, brain cancer, a leukemia, a lymphoma, bone cancer and pain associated with metastasis of a cancer.

23. The method of aspect 21, wherein the antibody or antigen-binding fragment is administered to the patient in combination with a second therapeutic agent.

24. The method of aspect 23, wherein the second therapeutic agent is selected from the group consisting of an opioid, a COX-2 inhibitor, a local anesthetic, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a second GFRα3 antagonist, a cytokine or cytokine receptor antagonist, a nerve growth factor (NGF) inhibitor (a small molecular inhibitor or an anti-NGF antibody), an inhibitor of BDNF, TrkA, TrkB or p75, aspirin, a NSAID, a steroid, morphine, a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a tricyclic, an inhibitor of a voltage-gated sodium channel (Na_v), a calcium channel inhibitor, a potassium channel inhibitor, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of GFRα1, GFRα2 or GFRα4, an inhibitor of an acid sensing ion channel (ASIC1 or ASIC3), an anti-convulsant (gabapentin or pregabalin), an inhibitor of a prekineticin receptor (PROK1 and PROK2), a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig and a corticosteroid.

25. The method of aspect 24, wherein the second GFRα3 antagonist is a small organic molecule, a polypeptide antagonist, a second antibody specific for GFRα3, a siRNA or an antisense molecule specific for GFRα3.

26. The method of aspect 24, wherein the cytokine or cytokine receptor antagonist is an interleukin-1 (IL-1) antagonist, an IL-6 antagonist, or an IL-18 antagonist.

27. A pharmaceutical composition comprising an antibody or antigen-binding fragment thereof according to any one of aspects 1 through 16 and a second therapeutic agent according to aspect 24 and a pharmaceutically acceptable carrier or diluent.

28. The isolated antibody or antigen-binding fragment thereof according to any one of aspects 1 through 16, or the pharmaceutical composition of either aspect 20 or 27, for use in treating a GFRα3-related condition or disease, or the pain associated with the GFRα3-related condition or disease, wherein the GFRα3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

29. The isolated antibody or antigen-binding fragment thereof for use according to aspect 28, wherein the GFRα3-related condition or disease is selected from the group consisting of acute pain, chronic pain, neuropathic pain, inflammatory pain, a functional pain syndrome, arthritis, pancreatitis, osteoarthritis, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, neurodegenerative disorders, movement disorders, neuroendocrine disorders, ataxia, visceral pain, gout, post-herpetic neuralgia, diabetic neuropathy, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, post-surgical pain, hereditary erythromelalgia, dental pain, rhinitis, cancer pain, complex regional pain syndrome (CRPS), inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and bladder disorders.

30. Use of the isolated antibody or antigen-binding fragment thereof according to any one of aspects 1 through 16, or the pharmaceutical composition of either of aspect 20 or 27, in the manufacture of a medicament for treating a GFRα3-related condition or disease, or the pain associated with the GFRα3-related condition or disease, wherein

the GFRα3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

31. The use of the isolated antibody or antigen-binding fragment thereof according to aspect 30, wherein the GFRα3-related condition or disease is selected from the group consisting of acute pain, chronic pain, neuropathic pain, inflammatory pain, a functional pain syndrome, arthritis, pancreatitis, osteoarthritis, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, neurodegenerative disorders, movement disorders, neuroendocrine disorders, ataxia, visceral pain, gout, post-herpetic neuralgia, diabetic neuropathy, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, post-surgical pain, hereditary erythromelalgia, dental pain, rhinitis, cancer pain, complex regional pain syndrome (CRPS), inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and bladder disorders.

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            100                 105                 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> 35
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 35
ggattcacct ttagcagtta tgcc 24

<210> 36
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 36
Gly Phe Thr Phe Ser Ser Tyr Ala
 1   5

<210> 37
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 37
attagtggta gtggtaccag caca 24

<210> 38
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 38
Ile Ser Gly Ser Gly Thr Ser Thr
 1   5

<210> 39
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 39
tcgaaacctt ctgcattacg atttttacat tggttagcta tggacgtc 48

<210> 40
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 40
Ser Lys Pro Ser Ala Leu Arg Phe Leu His Trp Leu Ala Met Asp Val
1 5 10 15

<210> 41
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 41
gacatccaga tgacccagtc tccatcctca ctgtctgcat ttgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattagg aattatttag actggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcatccaatt tgcaaagtgg ggtcccatca 180
aggttcggcg gcagtggatc tgggacagat ttcactctca ccatcaacag cctgcagcct 240
gaagattttg taacttatta ctgccagcag tataattctt accctcccac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 42
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 42
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Phe Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr
20 25 30
Leu Asp Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45
Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Gly Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Val Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 43
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43
caggacatta ggaattat 18

<210> 44
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 44
Gln Asp Ile Arg Asn Tyr
1 5

<210> 45
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 45
gctgcatcc 9

<210> 46
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46
Ala Ala Ser
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<210> 47
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 47
cagcagtata attcttaccc tcccact 27

<210> 48
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48
Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 49
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 49
caggttcaac tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggtta cacctttacc agctatggta tcatctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaatggtaa cacaaactat 180
gcacagaatc tccagggcag agtcaccatg accacagaca cttccacgac cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagatggggt 300
atagcaactc gtccctacta ctactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 50
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 50
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Gly Ile Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Ile Ser Gly Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Asn Leu
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Thr Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Gly Ile Ala Thr Arg Pro Tyr Tyr Tyr Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 51
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 51
ggttacacct ttaccagcta tggt 24

<210> 52
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 52
Gly Tyr Thr Phe Thr Ser Tyr Gly
1 5

<210> 53
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 53
atcagcggtt acaatggtaa caca 24

<210> 54
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 54
Ile Ser Gly Tyr Asn Gly Asn Thr
1 5

<210> 55
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 55
gcgagatggg gtatagcaac tcgtccctac tactactacg gtatggacgt c 51

<210> 56
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56
Ala Arg Trp Gly Ile Ala Thr Arg Pro Tyr Tyr Tyr Tyr Gly Met Asp

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 1               5                  10                  15
Val
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<210> 57
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 57
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattacc aattatttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tataatagtt accctcccac tttcggccct 300
gggaccaaag tggatatcaa a   321

<210> 58
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 58

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Thr Asn Tyr
            20                  25                  30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
                85                  90                  95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105
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<210> 59
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 59
caggacatta ccaattat   18

<210> 60
<211> 6
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 60
Gln Asp Ile Thr Asn Tyr
1 5

<210> 61
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 61
gctgcatcc 9

<210> 62
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 62
Ala Ala Ser
1

<210> 63
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 63
caacagtata atagttaccc tcccact 27

<210> 64
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 64
Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 65
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 65
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc cgggggggtc cctgagagtc 60
tcctgtgcag cctctggatt cacctttagc acctctgcca tgagctgggt ccgccaggct 120
ccagggaagg ggcttgagtg ggtctcaggt attagtggta ttggaggtgg tagcacatac 180
tacgcagact ccgtgaaggg ccggttcacc atctccagag acaattccaa gaacacgctg 240
tatctgcaaa tgaacagcct gagagccgag gacacggccg tatatttctg tgcgaaattt 300
tataagtgga attcatatat ttttgatctc tggggccagg ggacaatggt caccgtctct 360
tca 363

<210> 66
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 66
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Val Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Ser
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Gly Ile Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
50 55 60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
85 90 95
Cys Ala Lys Phe Tyr Lys Trp Asn Ser Tyr Ile Phe Asp Leu Trp Gly
100 105 110
Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 67
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67
ggattcacct ttagcacctc tgcc 24

<210> 68
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 68
Gly Phe Thr Phe Ser Thr Ser Ala
1 5

<210> 69
<211> 27
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 69
attagtggta ttggaggtgg tagcaca 27

<210> 70
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 70
Ile Ser Gly Ile Gly Gly Gly Ser Thr
1 5

<210> 71
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 71
gcgaaatttt ataagtggaa ttcatatatt tttgatctc 39

<210> 72
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 72
Ala Lys Phe Tyr Lys Trp Asn Ser Tyr Ile Phe Asp Leu
1 5 10

<210> 73
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 73
gaaattgtgt tgacgcagtc tccagacacc ctatctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagt agcagctact ttgcctggta ccagcagaag 120
cctggccagg ctcccaggct cctcatgtat agtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttctctc tcaccatcag cagattggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta ggtcactcac tttcggcgga 300
gggaccaagg tggagatcaa g 321

<210> 74
<211> 107

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 74
Glu Ile Val Leu Thr Gln Ser Pro Asp Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30
Tyr Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Met Tyr Ser Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 75
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 75
cagagtgtta gtagcagcta c 21

<210> 76
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 76
Gln Ser Val Ser Ser Ser Tyr
1 5

<210> 77
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 77
agtgcatcc 9

<210> 78
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78
Ser Ala Ser
1

<210> 79
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 79
cagcagtatg gtaggtcact cact 24

<210> 80
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80
Gln Gln Tyr Gly Arg Ser Leu Thr
1 5

<210> 81
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 81
gaggtgcagc tgttggagtc tgggggaggc ttggtacagt ctgggggtc actgagactc 60
tcctgtgcag cctctggatt cagctttaac aactatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcattt attagtggta gtggtggtag tacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa tacgctgtat 240
ctgcaaatga acagcctgag agtcgaggac acggccgttt tttactgtgc gaaagacaga 300
tacaactatg gtaccttctt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 82
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 82
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Ser Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asn Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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        35                  40                  45
Ser Phe Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Phe Tyr Cys
                85                  90                  95
Ala Lys Asp Arg Tyr Asn Tyr Gly Thr Phe Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> 83
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 83
ggattcagct ttaacaacta tgcc 24

<210> 84
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 84
Gly Phe Ser Phe Asn Asn Tyr Ala
 1   5

<210> 85
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 85
attagtggta gtggtggtag taca 24

<210> 86
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 86
Ile Ser Gly Ser Gly Gly Ser Thr
 1   5

<210> 87
<211> 39

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 87
gcgaaagaca gatacaacta tggtaccttc tttgactac 39

<210> 88
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 88
Ala Lys Asp Arg Tyr Asn Tyr Gly Thr Phe Phe Asp Tyr
1 5 10

<210> 89
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 89
gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca aatccagcca gagtgtttta tacagctcca acaataagaa ctacttaact 120
tggtaccagc agaaaccagg acagcctcct aaattgctca tttactgggc atctacccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtact 300
cctccgacgt tcggcctagg gaccaaggtg gaaatcaaa 339

<210> 90
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 90
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30
Ser Asn Asn Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95
Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Leu Gly Thr Lys Val Glu Ile
100 105 110
Lys

<210> 91
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 91
cagagtgttt tatacagctc caacaataag aactac 36

<210> 92
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 92
Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 93
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 93
tgggcatct 9

<210> 94
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 94
Trp Ala Ser
1

<210> 95
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 95
cagcaatatt atagtactcc tccgacg 27

<210> 96
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 96
Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
 1   5

<210> 97
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 97
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tcctgtgcag cctctggatt cacctttagc aactatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatg tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaacccccg 300
agtagagcag ctcgatactt caactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca   372

<210> 98
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 98
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Glu
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Pro Pro Ser Arg Ala Ala Arg Tyr Phe Asn Tyr Gly Met Asp
            100   105   110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 99
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 99
ggattcacct ttagcaacta tgcc 24

<210> 100
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 100
Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> 101
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 101
attagtggta gtggtggtag caca 24

<210> 102
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 102
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 103
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 103
gcgaaacccc cgagtagagc agctcgatac ttcaactacg gtatggacgt c 51

<210> 104
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 104
Ala Lys Pro Pro Ser Arg Ala Ala Arg Tyr Phe Asn Tyr Gly Met Asp
1 5 10 15
Val

<210> 105
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 105
gccatccgga tgacccagtc cccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag gctaacagtt tcccgttcac tttcggcgga 300
gggaccaagg tggagatcaa a 321

<210> 106
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 106
Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 107
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107
cagggtatta gcagctgg 18

<210> 108
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 108
Gln Gly Ile Ser Ser Trp
1 5

<210> 109
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 109
gctgcatcc 9

<210> 110
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 110
Ala Ala Ser
1

<210> 111
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 111
caacaggcta acagtttccc gttcact 27

<210> 112
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 112
Gln Gln Ala Asn Ser Phe Pro Phe Thr
1 5

<210> 113
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 113
gaagtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccgggcaagg ggctggagtg ggtgtcattt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgac agccgaggac acggctgtat attattgtgc gagaagaggt 300
atcctaactg gaactaccgc ttttgatatc tggggccaag ggacaatggt caccgtctct 360
tca 363

<210> 114
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 114
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Phe Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Ile Leu Thr Gly Thr Thr Ala Phe Asp Ile Trp Gly
100 105 110
Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 115
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 115
ggattcacct tcagtagcta tggc 24

<210> 116
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 116
Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 117
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 117
atatggtatg atggaagtaa taaa 24

<210> 118
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 118
Ile Trp Tyr Asp Gly Ser Asn Lys
1 5

<210> 119
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 119
gcgagaagag gtatcctaac tggaactacc gcttttgata tc 42

<210> 120
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 120
Ala Arg Arg Gly Ile Leu Thr Gly Thr Thr Ala Phe Asp Ile
1 5 10

<210> 121
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 121
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtgggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc agttatttga attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatccggag tctgatacct 240
gaagattttg caacttacta ctgtcaacag acttacaata ccccattcac tttcggccct 300
gggaccaagg tggaaatcaa a 321

<210> 122
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 122
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Ser Leu Ile Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asn Thr Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
100 105

<210> 123
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 123
cagagcatta gcagttat 18

<210> 124
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 124
Gln Ser Ile Ser Ser Tyr
1 5

<210> 125
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 125
gctgcatcc 9

<210> 126
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 126
Ala Ala Ser
1

<210> 127
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 127
caacagactt acaatacccc attcact 27

<210> 128
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 128
Gln Gln Thr Tyr Asn Thr Pro Phe Thr
1 5

<210> 129
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
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<400> 129
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tcctgtgcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcatct atatggtttg atggaagtaa tgaactctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gttttggtag ctacctctgc ttttcatatc tggggccaag ggacaatggt caccgtctct 360
tca 363

<210> 130
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 130
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr
20 25 30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Leu Tyr Ala Asp Ser Val

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    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe His Ile Trp Gly
            100                 105                 110
Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120
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<210> 131
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 131
ggattcagtt tcagtgacta tgtc 24

<210> 132
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 132
Gly Phe Ser Phe Ser Asp Tyr Val
 1   5

<210> 133
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 133
atatggtttg atggaagtaa tgaa 24

<210> 134
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 134
Ile Trp Phe Asp Gly Ser Asn Glu
 1   5

<210> 135
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 135
gcgaaaaagg gagttttggt agctacctct gcttttcata tc 42

<210> 136
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 136
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe His Ile
1 5 10

<210> 137
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 137
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atcacttgcc gggcaagtca gaacattaac aactatttaa attggtatca tcagaaacca 120
gggaaagccc ctaatctcct aatttatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat tacactctca ccatcagcag tctgcaacct 240
gaagattttg gaaattacta ctgtcaacag agttacagca cttccatgta cacttttggc 300
caggggacca agctggagat caaa 324

<210> 138
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 138
Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Asn Asn Tyr
20 25 30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Ser Met
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 139
<211> 18

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 139
cagaacatta acaactat 18

<210> 140
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 140
Gln Asn Ile Asn Asn Tyr
1 5

<210> 141
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 141
gctgcatcc 9

<210> 142
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 142
Ala Ala Ser
1

<210> 143
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 143
caacagagtt acagcacttc catgtacact 30

<210> 144
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 144
Gln Gln Ser Tyr Ser Thr Ser Met Tyr Thr
 1   5   10

<210> 145
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 145
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt attagtggta gtggaggtag cacatactac 180
gcagacgccg tgaagggccg gttcaccatc tccagagaca attccaagca cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtac gaaaccctca 300
tcttatagca gttcgaactt ctattatggt atggacgtct ggggccaagg gtccacggtc 360
accgtctcct ca   372

<210> 146
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 146
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys His Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Thr Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
            100   105   110
Val Trp Gly Gln Gly Ser Thr Val Thr Val Ser Ser
        115   120

<210> 147
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 147
ggattcacct ttagcagcta tgcc   24

<210> 148

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 148
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 149
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 149
attagtggta gtggaggtag caca 24

<210> 150
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 150
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 151
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 151
acgaaaccct catcttatag cagttcgaac ttctattatg gtatggacgt c 51

<210> 152
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 152
Thr Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
1 5 10 15
Val

<210> 153

<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 153
gacatccagt tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcagcag actaacagtt tcccattccc tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 154
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 154
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Asn Ser Phe Pro Phe
85 90 95
Pro Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 155
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 155
cagggtatta gcagctgg 18

<210> 156
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 156
Gln Gly Ile Ser Ser Trp
1 5

<210> 157
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 157
gctgcatcc 9

<210> 158
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 158
Ala Ala Ser
1

<210> 159
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 159
cagcagacta acagtttccc attccct 27

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 160
Gln Gln Thr Asn Ser Phe Pro Phe Pro
1 5

<210> 161
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 161
gaggtgcagc tggtggagtc tgggggaggc ttggtacagg ctgggggtc cctgagactc 60
tcctgtgtag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactcc 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtac gaaaccctca 300

tcttatagca gctcgaactt ctactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 162
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 162

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Ala	Gly	Gly
1				5				10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
		20					25					30			
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35					40					45				
Ser	Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Ser	Ala	Asp	Ser	Val
50					55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65				70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90					95		
Thr	Lys	Pro	Ser	Ser	Tyr	Ser	Ser	Ser	Asn	Phe	Tyr	Tyr	Gly	Met	Asp
		100					105					110			
Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser				
	115					120									

<210> 163
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 163
ggattcacct ttagcagcta tgcc 24

<210> 164
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 164

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Ala
1				5			

<210> 165
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 165

attagtggta gtggtggtag caca 24

<210> 166
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 166
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 167
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 167
acgaaaccct catcttatag cagctcgaac ttctactacg gtatggacgt c 51

<210> 168
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 168
Thr Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
1 5 10 15
Val

<210> 169
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 169
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatact gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc taggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag actaacagtc tcccactcac tttcggccct 300
gggaccaagg tggagatcaa a 321

<210> 170
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 170

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Thr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Asn Ser Leu Pro Leu
                85                  90                  95
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 171
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 171
cagggtatta gcagctgg 18

<210> 172
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 172

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Gln Gly Ile Ser Ser Trp
 1               5
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<210> 173
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 173
actgcatcc 9

<210> 174
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 174

Thr Ala Ser
1

<210> 175
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 175
caacagacta acagtctccc actcact 27

<210> 176
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 176
Gln Gln Thr Asn Ser Leu Pro Leu Thr
1 5

<210> 177
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 177
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctacaaatga acagcctgag agccgaggac acggccgttt attactgtgc gaaaccctca 300
tcttatagca gctcgaactt ctactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 178
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 178
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 179
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 179
ggattcacct ttagcagcta tgcc 24

<210> 180
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 180
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 181
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 181
attagtggta gtggtggtag caca 24

<210> 182
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 182
Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 183
<211> 51
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 183
gcgaaaccct catcttatag cagctcgaac ttctactacg gtatggacgt c 51

<210> 184
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 184
Ala Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
1 5 10 15
Val

<210> 185
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 185
gacatcgtga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcgaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcaccag cctgcagcct 240
gaagattttg caacttacta ttgtcaacac actaacagtt tcccattcac tttcggccct 300
gggaccaagg tggagatcaa a 321

<210> 186
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 186
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Arg Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Thr Asn Ser Phe Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
100 105

<210> 187
<211> 18

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 187
cagggtatta gcagctgg 18

<210> 188
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 188
Gln Gly Ile Ser Ser Trp
1 5

<210> 189
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189
gctgcatcc 9

<210> 190
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 190
Ala Ala Ser
1

<210> 191
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 191
caacacacta acagtttccc attcact 27

<210> 192
<211> 9
<212> PRT
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<220>

<223> Synthetic

<400> 192
Gln His Thr Asn Ser Phe Pro Phe Thr
1 5

<210> 193
<211> 369
<212> DNA
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<220>
<223> Synthetic

<400> 193
gaggtgcagc tggtggagtc tggggctgag gtgaagaagt ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcagc cgctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatccctc tctttggtac attaaactac 180
gcacagaagt tccagggcag agtcacgctt accacggacg aatcaacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc ggtattttac 300
tatggttcgg ggagttatcg caactggttc gacccctggg gccagggaac cctggtcacc 360
gtctcctca 369

<210> 194
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 194
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Ser Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Arg Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Leu Phe Gly Thr Leu Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Leu Thr Thr Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Val Phe Tyr Tyr Gly Ser Gly Ser Tyr Arg Asn Trp Phe Asp Pro
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 195
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 195
ggaggcacct tcagccgcta tgct 24

<210> 196

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 196
Gly Gly Thr Phe Ser Arg Tyr Ala
1 5

<210> 197
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 197
atcatccctc tctttggtac atta 24

<210> 198
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 198
Ile Ile Pro Leu Phe Gly Thr Leu
1 5

<210> 199
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 199
gcggtatttt actatggttc ggggagttat cgcaactggt tcgacccc 48

<210> 200
<211> 16
<212> PRT
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<220>
<223> Synthetic

<400> 200
Ala Val Phe Tyr Tyr Gly Ser Gly Ser Tyr Arg Asn Trp Phe Asp Pro
1 5 10 15

<210> 201
<211> 321
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 201
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcatcagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacca ctgtcaacag agttacagta tcccgatcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 202
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 202
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr His Cys Gln Gln Ser Tyr Ser Ile Pro Ile
85 90 95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 203
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 203
cagagcatca gcagctat 18

<210> 204
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 204
Gln Ser Ile Ser Ser Tyr
1 5

<210> 205

<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 205
gctgcatcc 9

<210> 206
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 206
Ala Ala Ser
1

<210> 207
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 207
caacagagtt acagtatccc gatcacc 27

<210> 208
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 208
Gln Gln Ser Tyr Ser Ile Pro Ile Thr
1 5

<210> 209
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 209
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc acctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggaatg ggtctcagct attcgtggta atggtgttaa cacatactac 180
ggagactcca tgaagggccg tttcaccatc tccagagaca attccaagga cacgctgtat 240
ttgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaaataaa 300
tgggagctgc tagtctttga atactggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 210
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 210
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Arg Gly Asn Gly Val Asn Thr Tyr Tyr Gly Asp Ser Met
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asn Lys Trp Glu Leu Leu Val Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 211
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 211
ggattcacct ttagcaccta tgcc 24

<210> 212
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 212
Gly Phe Thr Phe Ser Thr Tyr Ala
1 5

<210> 213
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 213
attcgtggta atggtgttaa caca 24

<210> 214

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 214
Ile Arg Gly Asn Gly Val Asn Thr
1 5

<210> 215
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 215
gcgaaaaata aatgggagct gctagtcttt gaatac 36

<210> 216
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 216
Ala Lys Asn Lys Trp Glu Leu Leu Val Phe Glu Tyr
1 5 10

<210> 217
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 217
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtca ggacattagc aattatttag cctggtatca gcagaaacca 120
gggaaagttc ctaagctcct gatctatgct gcatccactt tgcaatcagg ggtcccattt 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagatgttg caacttatta ctgtcaaaag tataacagtg cccctccttt cggccctggg 300
accaaagtgg atatcaaa 318

<210> 218
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 218
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Phe Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Pro
85 90 95
Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 219
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 219
caggacatta gcaattat 18

<210> 220
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 220
Gln Asp Ile Ser Asn Tyr
1 5

<210> 221
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 221
gctgcatcc 9

<210> 222
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 222
Ala Ala Ser
1

<210> 223

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 223
caaaagtata acagtgcccc tcct 24

<210> 224
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 224
Gln Lys Tyr Asn Ser Ala Pro Pro
1 5

<210> 225
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 225
gaggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcatct atatggtttg atggaagtaa tgaattctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gtgttggtag ctacctctgc ttttgatatc tggggccaag ggacaatggt caccgtctct 360
tca 363

<210> 226
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 226
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr
20 25 30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Phe Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 227
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 227
ggattcagtt tcagtgacta tgtc 24

<210> 228
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 228
Gly Phe Ser Phe Ser Asp Tyr Val
1 5

<210> 229
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 229
atatggtttg atggaagtaa tgaa 24

<210> 230
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 230
Ile Trp Phe Asp Gly Ser Asn Glu
1 5

<210> 231
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 231
gcgaaaaagg gagtgttggt agctacctct gcttttgata tc 42

<210> 232
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 232
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile
1 5 10

<210> 233
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 233
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattaac aactatttaa attggtatca tcagaaacca 120
gggaaagccc ctaagctcct aatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat tacactctca ccatcagcag tctgcaacct 240
gaagattttg gaaattacta ctgtcaacag agttacagaa cttccatgta cacttttggc 300
caggggacca aggtggaaat caaa 324

<210> 234
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 234
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr
20 25 30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Ser Met
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 235
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 235

cagagcatta acaactat 18

<210> 236
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 236
Gln Ser Ile Asn Asn Tyr
1 5

<210> 237
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 237
gctgcatcc 9

<210> 238
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 238
Ala Ala Ser
1

<210> 239
<211> 30
<212> DNA
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<220>
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<400> 239
caacagagtt acagaacttc catgtacact 30

<210> 240
<211> 10
<212> PRT
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<220>
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<400> 240
Gln Gln Ser Tyr Arg Thr Ser Met Tyr Thr
1 5 10

<210> 241
<211> 360
<212> DNA
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<220>
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<400> 241
gaggtgcagc tggtggagtc tgggggaggc ttggtacggc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat aattatgcca tgcactgggt ccggcaagtt 120
ccagggaagg gcctggagtg ggtctcaggt attacttgga atagtgttag cctaggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgcccagaa ctccctgtat 240
ctgcaaatga acagtctgag aactgtggac acggccttgt attactgtgc aaaagatagg 300
tggggtggaa gttactactt tgacttctgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 242
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 242
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Arg Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asn Tyr
            20   25   30
Ala Met His Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gly Ile Thr Trp Asn Ser Val Ser Leu Gly Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Ser Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Thr Val Asp Thr Ala Leu Tyr Tyr Cys
                85   90   95
Ala Lys Asp Arg Trp Gly Gly Ser Tyr Tyr Phe Asp Phe Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 243
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 243
ggattcacct ttgataatta tgcc 24

<210> 244
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 244
Gly Phe Thr Phe Asp Asn Tyr Ala
1 5

<210> 245
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 245
attacttgga atagtgttag ccta 24

<210> 246
<211> 8
<212> PRT
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<220>
<223> Synthetic

<400> 246
Ile Thr Trp Asn Ser Val Ser Leu
1 5

<210> 247
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 247
gcaaaagata ggtggggtgg aagttactac tttgacttc 39

<210> 248
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<400> 248
Ala Lys Asp Arg Trp Gly Gly Ser Tyr Tyr Phe Asp Phe
1 5 10

<210> 249
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
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<400> 249
gacatcgtga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca gggcattagc aattatttag cctggtatca gcagaaacca 120
gggaaagttc ctaaactcct gatctattct gcatccactt tgcaatcagg ggtcccatct 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcaa cctgcagcct 240
gaagattttg caacttttt ctgtcaaaag tataacagtg cccccacttt cggcggaggg 300
accaaggtgg agatcaaa 318

<210> 250
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 250
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Phe Phe Cys Gln Lys Tyr Asn Ser Ala Pro Thr
85 90 95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 251
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 251
cagggcatta gcaattat 18

<210> 252
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 252
Gln Gly Ile Ser Asn Tyr
1 5

<210> 253
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 253
tctgcatcc 9

<210> 254
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 254
Ser Ala Ser
1

<210> 255
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 255
caaaagtata acagtgcccc cact 24

<210> 256
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 256
Gln Lys Tyr Asn Ser Ala Pro Thr
1 5

<210> 257
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 257
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcatct atatggtttg atggaagtaa tgaattctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gtgttggtag ctacctctgc ttttgatatc tggggccaag ggacaatggt caccgtctct 360
tca 363

<210> 258
<211> 121
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 258

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr
            20                  25                  30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Phe Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile Trp Gly
            100                 105                 110
Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120
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<210> 259
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 259
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<210> 260
<211> 8
<212> PRT
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<220>
<223> Synthetic

<400> 260

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Gly Phe Ser Phe Ser Asp Tyr Val
 1               5
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<210> 261
<211> 24
<212> DNA
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<220>
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<400> 261
atatggtttg atggaagtaa tgaa 24

<210> 262
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 262
Ile Trp Phe Asp Gly Ser Asn Glu
 1   5

<210> 263
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 263
gcgaaaaagg gagtgttggt agctacctct gcttttgata tc 42

<210> 264
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 264
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile
 1   5   10

<210> 265
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 265
gaaattgtga tgacgcagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattaac aactatttaa attggtatca tcagaaacca 120
gggaaagccc ctaagctcct aatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat tacactctca ccatcagcag tctgcaacct 240
gaagattttg gaaattacta ctgtcaacag agttacagaa cttccatgta cacttttggc 300
caggggacca aggtggagat caaa 324

<210> 266
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 266
Glu Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr
            20   25   30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Ser Met
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 267
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 267
cagagcatta acaactat 18

<210> 268
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 268
Gln Ser Ile Asn Asn Tyr
1 5

<210> 269
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 269
gctgcatcc 9

<210> 270
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 270
Ala Ala Ser
1

<210> 271
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 271
caacagagtt acagaacttc catgtacact 30

<210> 272
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 272
Gln Gln Ser Tyr Arg Thr Ser Met Tyr Thr
1 5 10

<210> 273
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 273
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt acttactact ggagctggtt ccggcagccc 120
ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caaccacaac 180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aaactgaggt ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag agtaggtccg 300
gtgggctggg gatcatgggg gaactttgac tactggggcc agggaaccct ggtcaccgtc 360
tcctca 366

<210> 274
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 274
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Thr Tyr
20 25 30
Tyr Trp Ser Trp Phe Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn His Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Val Gly Pro Val Gly Trp Gly Ser Trp Gly Asn Phe Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 275
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 275
ggtggctcca tcagtactta ctac 24

<210> 276
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 276
Gly Gly Ser Ile Ser Thr Tyr Tyr
1 5

<210> 277
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 277
atctattaca gtgggagcac c 21

<210> 278
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 278
Ile Tyr Tyr Ser Gly Ser Thr
1 5

<210> 279
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 279
gcgagagtag gtccggtggg ctggggatca tgggggaact ttgactac 48

<210> 280
<211> 16
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 280
Ala Arg Val Gly Pro Val Gly Trp Gly Ser Trp Gly Asn Phe Asp Tyr
1 5 10 15

<210> 281
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 281
gacatccagt tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtca gggcattagc agttatttag cctggtctca gcaaaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccactt tacaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatagtt acccgtggac gttcggccaa 300
gggaccaagg tggagatcaa a 321

<210> 282
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 282
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30
Leu Ala Trp Ser Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 283
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 283
cagggcatta gcagttat 18

<210> 284
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 284
Gln Gly Ile Ser Ser Tyr
1 5

<210> 285
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 285
gctgcatcc 9

<210> 286
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 286
Ala Ala Ser
1

<210> 287
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 287
caacagctta atagttaccc gtggacg 27

<210> 288
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 288
Gln Gln Leu Asn Ser Tyr Pro Trp Thr
1 5

<210> 289
<211> 360
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 289
gaggtgcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggtta cacctttacc aattatggta tcacctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatggggtgg atcagcgctt acaatggtaa caccggctat 180
gcacagaaat tccagggcag agtcaccatg accacagaca cttccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggat 300
tacgattttt ggagggcttt tgatatctgg ggccaaggga caatggtcac cgtctcttca 360

<210> 290
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 290
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20   25   30
Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Glu Asp Tyr Asp Phe Trp Arg Ala Phe Asp Ile Trp Gly Gln
            100   105   110
Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 291
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 291
ggttacacct ttaccaatta tggt 24

<210> 292
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 292
Gly Tyr Thr Phe Thr Asn Tyr Gly
 1   5

<210> 293

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 293
atcagcgctt acaatggtaa cacc 24

<210> 294
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 294
Ile Ser Ala Tyr Asn Gly Asn Thr
1 5

<210> 295
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 295
gcgagagagg attacgattt ttggagggct tttgatatc 39

<210> 296
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 296
Ala Arg Glu Asp Tyr Asp Phe Trp Arg Ala Phe Asp Ile
1 5 10

<210> 297
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 297
gaaattgtgc tgactcagtc tccaggcacc ctgtctttgt ctccggggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcacctact tagcctggct ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac cggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcaa cagactggag 240
cctgaagatt ttgcagtgta ttattgtcaa cagtatgctt actcaccgta cacttttggc 300
caggggacca agctggagat caaa 324

<210> 298
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 298
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30
Tyr Leu Ala Trp Leu Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ala Tyr Ser Pro
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 299
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 299
cagagtgtta gcagcaccta c 21

<210> 300
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 300
Gln Ser Val Ser Ser Thr Tyr
1 5

<210> 301
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 301
ggtgcatcc 9

<210> 302
<211> 3
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 302
Gly Ala Ser
1

<210> 303
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 303
caacagtatg cttactcacc gtacact 27

<210> 304
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 304
Gln Gln Tyr Ala Tyr Ser Pro Tyr Thr
1 5

<210> 305
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 305
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcatct atatggtttg atggaagtaa tgaattctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gtgttggtag ctacctctgc ttttgatatc tggggccaag ggacaatggt caccgtctct 360
tca 363

<210> 306
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 306
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr

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            20                  25                  30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Phe Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile Trp Gly
            100                 105                 110
Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120
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<210> 307
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 307
ggattcagtt tcagtgacta tgtc 24

<210> 308
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 308
Gly Phe Ser Phe Ser Asp Tyr Val
 1   5

<210> 309
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 309
atatggtttg atggaagtaa tgaa 24

<210> 310
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 310
Ile Trp Phe Asp Gly Ser Asn Glu
 1   5

<210> 311
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 311
gcgaaaaagg gagtgttggt agctacctct gcttttgata tc 42

<210> 312
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 312
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile
1 5 10

<210> 313
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 313
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atcacttgcc gggcaagtca gagcattaac aactatttaa attggtatca tcagaaacca 120
gggaaagccc ctaagctcct aatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat tacactctca ccatcagcag tctgcaacct 240
gaagattttg gaaattacta ctgtcaacag agttacagaa cttccatgta cacttttggc 300
caggggacca aggtggaaat caaa 324

<210> 314
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 314
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr
20 25 30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Ser Met
85 90 95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 315
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 315
cagagcatta acaactat 18

<210> 316
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 316
Gln Ser Ile Asn Asn Tyr
1 5

<210> 317
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 317
gctgcatcc 9

<210> 318
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 318
Ala Ala Ser
1

<210> 319
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 319
caacagagtt acagaacttc catgtacact 30

<210> 320
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 320
Gln Gln Ser Tyr Arg Thr Ser Met Tyr Thr
 1   5   10

<210> 321
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 321
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tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggtt 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtgataa tacatataac 180
gcagagtccg tgaagggccg gttcaccatc tccagagaca attccaagaa tatgttgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaacaaag 300
tttagcagct cgttgctctt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

<210> 322
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 322
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30
Ala Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ala Ile Ser Gly Ser Gly Asp Asn Thr Tyr Asn Ala Glu Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Met Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Thr Lys Phe Ser Ser Ser Leu Leu Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 323
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 323
ggattcacct ttagcagcta tgcc 24

<210> 324
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 324
Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 325
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 325
attagtggta gtggtgataa taca 24

<210> 326
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 326
Ile Ser Gly Ser Gly Asp Asn Thr
1 5

<210> 327
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 327
gcgaaaacaa agtttagcag ctcgttgctc tttgactac 39

<210> 328
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 328
Ala Lys Thr Lys Phe Ser Ser Ser Leu Leu Phe Asp Tyr
1 5 10

<210> 329
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 329
gacatcgtga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gagtattagt tggtggttgg cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatagtt attccacttt cggcggaggg 300
accaagctgg agatcaaa 318

<210> 330
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 330
Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Trp Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Thr
85 90 95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 331
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 331
cagagtatta gttggtgg 18

<210> 332
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 332
Gln Ser Ile Ser Trp Trp

1 5

<210> 333
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 333
aaggcgtct 9

<210> 334
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 334
Lys Ala Ser
1

<210> 335
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 335
caacagtata atagttattc cact 24

<210> 336
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 336
Gln Gln Tyr Asn Ser Tyr Ser Thr
1 5

<210> 337
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 337
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctacatt cacctttagc agctatgcca tgacctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaagt attagtggta gtggtgatag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaaaggat 300
gggcctggga ggtattacgt gaggtacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 338
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 338
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Thr Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Lys Asp Gly Pro Gly Arg Tyr Tyr Val Arg Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 339
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 339
acattcacct ttagcagcta tgcc 24

<210> 340
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 340
Thr Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 341
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 341
attagtggta gtggtgatag caca 24

<210> 342
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 342
Ile Ser Gly Ser Gly Asp Ser Thr
1 5

<210> 343
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 343
gcgaaaaagg atgggcctgg gaggtattac gtgaggtacg gtatggacgt c 51

<210> 344
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 344
Ala Lys Lys Asp Gly Pro Gly Arg Tyr Tyr Val Arg Tyr Gly Met Asp
1 5 10 15
Val

<210> 345
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 345
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatact acatccagtt tgcaaagtgg ggtcccatcc 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ttgtcaacag gctaacagtt tccctctcac tttcggcgga 300
gggaccaaag tggatatcaa a 321

<210> 346
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 346
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Thr Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys
100 105

<210> 347
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 347
cagggtatta gcagctgg 18

<210> 348
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 348
Gln Gly Ile Ser Ser Trp
1 5

<210> 349
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 349
actacatcc 9

<210> 350
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 350
Thr Thr Ser
1

<210> 351
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 351
caacaggcta acagtttccc tctcact 27

<210> 352
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 352
Gln Gln Ala Asn Ser Phe Pro Leu Thr
1 5

<210> 353
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 353
gaggtgcagc tggtggagtc tgggggaggc ttggaacagc ctgggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgtca tgagctgggt ccgccaggtt 120
ccagggaagg ggctggagtg ggtctcagtt atcagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaccctca 300
tcttatagca gctcgaactt ccactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 354
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 354
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Glu Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Val Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

```
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe His Tyr Gly Met Asp
            100                 105                 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 355
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 355
ggattcacct ttagcagcta tgtc 24

<210> 356
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 356
Gly Phe Thr Phe Ser Ser Tyr Val
 1   5

<210> 357
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 357
atcagtggta gtggtggtag caca 24

<210> 358
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 358
Ile Ser Gly Ser Gly Gly Ser Thr
 1   5

<210> 359
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 359
gcgaaaccct catcttatag cagctcgaac ttccactacg gtatggacgt c 51

<210> 360
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 360
Ala Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe His Tyr Gly Met Asp
1 5 10 15
Val

<210> 361
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 361
gacatccaga tgacccagtc tccatattcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggagagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaaaag actaacagtt tcccattcac tttcggccct 300
gggaccaagg tggaaatcaa a 321

<210> 362
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 362
Asp Ile Gln Met Thr Gln Ser Pro Tyr Ser Val Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Thr Asn Ser Phe Pro Phe
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
100 105

<210> 363
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 363
cagggtatta gcagctgg 18

<210> 364
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 364
Gln Gly Ile Ser Ser Trp
1 5

<210> 365
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 365
gctgcatcc 9

<210> 366
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 366
Ala Ala Ser
1

<210> 367
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 367
caaaagacta acagtttccc attcact 27

<210> 368
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 368
Gln Lys Thr Asn Ser Phe Pro Phe Thr
1 5

<210> 369
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 369
Ala Gly Gly Pro Gly Ser Arg Ala Arg Ala Ala Gly Ala Arg Gly Cys
1 5 10 15
Arg Leu Arg Ser Gln Leu Val Pro Val Arg Ala Leu Gly Leu Gly His
20 25 30
Arg Ser Asp Glu Leu Val Arg Phe Arg Phe Cys Ser Gly Ser Cys Arg
35 40 45
Arg Ala Arg Ser Pro His Asp Leu Ser Leu Ala Ser Leu Leu Gly Ala
50 55 60
Gly Ala Leu Arg Pro Pro Pro Gly Ser Arg Pro Val Ser Gln Pro Cys
65 70 75 80
Cys Arg Pro Thr Arg Tyr Glu Ala Val Ser Phe Met Asp Val Asn Ser
85 90 95
Thr Trp Arg Thr Val Asp Arg Leu Ser Ala Thr Ala Cys Gly Cys Leu
100 105 110
Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gly Gly Glu Gln Lys
115 120 125
Leu Ile Ser Glu Glu Asp Leu His His His His His His
130 135 140

<210> 370
<211> 371
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 370
Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala
1 5 10 15
Arg Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His
20 25 30
Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu
35 40 45
Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn
50 55 60
Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val
65 70 75 80
Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly
85 90 95
Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
100 105 110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
115 120 125

```
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys
    130                 135                 140
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys
145                 150                 155                 160
Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala
                165                 170                 175
Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn
            180                 185                 190
Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Asn Cys
        195                 200                 205
Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys
    210                 215                 220
Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His
225                 230                 235                 240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
                245                 250                 255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
            260                 265                 270
Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg
        275                 280                 285
Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Met Leu Glu Gly Phe Phe
    290                 295                 300
Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe
305                 310                 315                 320
His Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val
                325                 330                 335
Met Ala His Gln Asn Glu Asn Glu Gln Lys Leu Ile Ser Glu Glu Asp
            340                 345                 350
Leu Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu His His His
        355                 360                 365
His His His
    370
```

<210> 371
<211> 578
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 371

```
Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala
 1               5                  10                  15
Arg Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His
            20                  25                  30
Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu
        35                  40                  45
Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn
    50                  55                  60
Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val
65                  70                  75                  80
Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly
                85                  90                  95
Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
            100                 105                 110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
        115                 120                 125
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys
    130                 135                 140
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys
145                 150                 155                 160
```

```
Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala
                165                 170                 175
Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn
            180                 185                 190
Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Asn Cys
        195                 200                 205
Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys
    210                 215                 220
Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His
225                 230                 235                 240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
                245                 250                 255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
            260                 265                 270
Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg
        275                 280                 285
Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Met Leu Glu Gly Phe Phe
    290                 295                 300
Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe
305                 310                 315                 320
His Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val
                325                 330                 335
Met Ala His Gln Asn Glu Asn Pro Ala Val Arg Pro Gln Pro Trp Asp
            340                 345                 350
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        355                 360                 365
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    370                 375                 380
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
385                 390                 395                 400
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                405                 410                 415
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            420                 425                 430
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        435                 440                 445
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    450                 455                 460
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
465                 470                 475                 480
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                485                 490                 495
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            500                 505                 510
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        515                 520                 525
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    530                 535                 540
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
545                 550                 555                 560
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                565                 570                 575
Gly Lys
```

<210> 372
<211> 584
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 372

```
Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala
 1               5                  10                  15
Arg Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His
            20                  25                  30
Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu
        35                  40                  45
Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn
    50                  55                  60
Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val
65                  70                  75                  80
Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly
                85                  90                  95
Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
            100                 105                 110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
        115                 120                 125
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys
    130                 135                 140
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys
145                 150                 155                 160
Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala
                165                 170                 175
Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn
            180                 185                 190
Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Asn Cys
        195                 200                 205
Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys
    210                 215                 220
Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His
225                 230                 235                 240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
                245                 250                 255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
            260                 265                 270
Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg
        275                 280                 285
Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Met Leu Glu Gly Phe Phe
    290                 295                 300
Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe
305                 310                 315                 320
His Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val
                325                 330                 335
Met Ala His Gln Asn Glu Asn Pro Ala Val Arg Pro Gln Pro Trp Glu
            340                 345                 350
Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala
        355                 360                 365
Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
    370                 375                 380
Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val
385                 390                 395                 400
Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val
                405                 410                 415
Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp
            420                 425                 430
Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
        435                 440                 445
Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp
    450                 455                 460
Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val
465                 470                 475                 480
Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr
```

```
                485                 490                 495
Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu
            500                 505                 510
Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr
        515                 520                 525
Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr
    530                 535                 540
Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr
545                 550                 555                 560
Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys
                565                 570                 575
Ser Phe Ser Arg Thr Pro Gly Lys
            580
```

<210> 373
<211> 371
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 373

```
Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala
 1               5                  10                  15
Arg Arg Lys Cys Gln Ala Asp Pro Ile Cys Ser Ala Ala Tyr His His
            20                  25                  30
Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu
        35                  40                  45
Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn
    50                  55                  60
Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val
65                  70                  75                  80
Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly
                85                  90                  95
Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
            100                 105                 110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
        115                 120                 125
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys
    130                 135                 140
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys
145                 150                 155                 160
Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala
                165                 170                 175
Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn
            180                 185                 190
Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Ser Cys
        195                 200                 205
Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys
    210                 215                 220
Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His
225                 230                 235                 240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
                245                 250                 255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
            260                 265                 270
Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg
        275                 280                 285
Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Gln Leu Glu Gly Phe Phe
    290                 295                 300
Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe
```

```
305                 310                 315                 320
His Ser Gln Leu Phe Tyr Gln Asp Trp Pro His Pro Thr Phe Ala Val
                325                 330                 335
Met Ala His Gln Asn Glu Asn Glu Gln Lys Leu Ile Ser Glu Glu Asp
            340                 345                 350
Leu Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu His His His
        355                 360                 365
His His His
    370
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<210> 374
<211> 1200
<212> DNA
<213> Homo sapiens

<400> 374
atggtgcgcc ccctgaaccc gcgaccgctg ccgcccgtag tcctgatgtt gctgctgctg 60
ctgccgccgt cgccgctgcc tctcgcagcc ggagaccccc ttcccacaga aagccgactc 120
atgaacagct gtctccaggc caggaggaag tgccaggctg atcccacctg cagtgctgcc 180
taccaccacc tggattcctg cacctctagc ataagcaccc cactgccctc agaggagcct 240
tcggtccctg ctgactgcct ggaggcagca cagcaactca ggaacagctc tctgataggc 300
tgcatgtgcc accggcgcat gaagaaccag gttgcctgct tggacatcta ttggaccgtt 360
caccgtgccc gcagccttgg taactatgag ctggatgtct ccccctatga agacacagtg 420
accagcaaac cctggaaaat gaatctcagc aaactgaaca tgctcaaacc agactcagac 480
ctctgcctca agtttgccat gctgtgtact ctcaatgaca agtgtgaccg gctgcgcaag 540
gcctacgggg aggcgtgctc cgggccccac tgccagcgcc acgtctgcct caggcagctg 600
ctcactttct tcgagaaggc cgccgagccc cacgcgcagg gcctgctact gtgcccatgt 660
gcccccaacg accggggctg cggggagcgc cggcgcaaca ccatcgcccc caactgcgcg 720
ctgccgcctg tggcccccaa ctgcctggag ctgcggcgcc tctgcttctc cgacccgctt 780
tgcagatcac gcctggtgga tttccagacc cactgccatc ccatggacat cctaggaact 840
tgtgcaacag agcagtccag atgtctacga gcatacctgg ggctgattgg gactgccatg 900
acccccaact ttgtcagcaa tgtcaacacc agtgttgcct taagctgcac ctgccgaggc 960
agtggcaacc tgcaggagga gtgtgaaatg ctggaagggt tcttctccca caacccctgc 1020
ctcacggagg ccattgcagc taagatgcgt tttcacagcc aactcttctc ccaggactgg 1080
ccacacccta cctttgctgt gatggcacac cagaatgaaa accctgctgt gaggccacag 1140
ccctgggtgc cctctctttt ctcctgcacg cttcccttga ttctgctcct gagcctatgg 1200

<210> 375
<211> 400
<212> PRT
<213> Homo sapiens

<400> 375
```
Met Val Arg Pro Leu Asn Pro Arg Pro Leu Pro Pro Val Val Leu Met
 1               5                  10                  15
Leu Leu Leu Leu Leu Pro Pro Ser Pro Leu Pro Leu Ala Ala Gly Asp
            20                  25                  30
Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala Arg
        35                  40                  45
Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His Leu
    50                  55                  60
Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu Pro
65                  70                  75                  80
Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn Ser
                85                  90                  95
Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val Ala
            100                 105                 110
Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly Asn
        115                 120                 125
Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys Pro
    130                 135                 140
```

```
Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser Asp
145                 150                 155                 160
Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys Asp
                165                 170                 175
Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys Gln
            180                 185                 190
Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala Ala
        195                 200                 205
Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn Asp
    210                 215                 220
Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Asn Cys Ala
225                 230                 235                 240
Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys Phe
                245                 250                 255
Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His Cys
            260                 265                 270
His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg Cys
        275                 280                 285
Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn Phe
    290                 295                 300
Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg Gly
305                 310                 315                 320
Ser Gly Asn Leu Gln Glu Glu Cys Glu Met Leu Glu Gly Phe Phe Ser
                325                 330                 335
His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe His
            340                 345                 350
Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val Met
        355                 360                 365
Ala His Gln Asn Glu Asn Pro Ala Val Arg Pro Gln Pro Trp Val Pro
    370                 375                 380
Ser Leu Phe Ser Cys Thr Leu Pro Leu Ile Leu Leu Leu Ser Leu Trp
385                 390                 395                 400
```

<210> 376
<211> 632
<212> PRT
<213> Homo sapiens

<400> 376

```
Asp Arg Leu Asp Cys Val Lys Ala Ser Asp Gln Cys Leu Lys Glu Gln
 1               5                  10                  15
Ser Cys Ser Thr Lys Tyr Arg Thr Leu Arg Gln Cys Val Ala Gly Lys
            20                  25                  30
Glu Thr Asn Phe Ser Leu Ala Ser Gly Leu Glu Ala Lys Asp Glu Cys
        35                  40                  45
Arg Ser Ala Met Glu Ala Leu Lys Gln Lys Ser Leu Tyr Asn Cys Arg
    50                  55                  60
Cys Lys Arg Gly Met Lys Lys Glu Lys Asn Cys Leu Arg Ile Tyr Trp
65                  70                  75                  80
Ser Met Tyr Gln Ser Leu Gln Gly Asn Asp Leu Leu Glu Asp Ser Pro
                85                  90                  95
Tyr Glu Pro Val Asn Ser Arg Leu Ser Asp Ile Phe Arg Val Val Pro
            100                 105                 110
Phe Ile Ser Asp Val Phe Gln Gln Val Glu His Ile Pro Lys Gly Asn
        115                 120                 125
Asn Cys Leu Asp Ala Ala Lys Ala Cys Asn Leu Asp Asp Ile Cys Lys
    130                 135                 140
Lys Tyr Arg Ser Ala Tyr Ile Thr Pro Cys Thr Thr Ser Val Ser Asn
145                 150                 155                 160
Asp Val Cys Asn Arg Arg Lys Cys His Lys Ala Leu Arg Gln Phe Phe
                165                 170                 175
Asp Lys Val Pro Ala Lys His Ser Tyr Gly Met Leu Phe Cys Ser Cys
```

```
            180                 185                 190
Arg Asp Ile Ala Cys Thr Glu Arg Arg Arg Gln Thr Ile Val Pro Val
        195                 200                 205
Cys Ser Tyr Glu Glu Arg Glu Lys Pro Asn Cys Leu Asn Leu Gln Asp
    210                 215                 220
Ser Cys Lys Thr Asn Tyr Ile Cys Arg Ser Arg Leu Ala Asp Phe Phe
225                 230                 235                 240
Thr Asn Cys Gln Pro Glu Ser Arg Ser Val Ser Ser Cys Leu Lys Glu
                245                 250                 255
Asn Tyr Ala Asp Cys Leu Leu Ala Tyr Ser Gly Leu Ile Gly Thr Val
            260                 265                 270
Met Thr Pro Asn Tyr Ile Asp Ser Ser Ser Leu Ser Val Ala Pro Trp
        275                 280                 285
Cys Asp Cys Ser Asn Ser Gly Asn Asp Leu Glu Glu Cys Leu Lys Phe
    290                 295                 300
Leu Asn Phe Phe Lys Asp Asn Thr Cys Leu Lys Asn Ala Ile Gln Ala
305                 310                 315                 320
Phe Gly Asn Gly Ser Asp Val Thr Val Trp Gln Pro Ala Phe Pro Val
                325                 330                 335
Gln Thr Thr Thr Ala Thr Thr Thr Thr Ala Leu Arg Val Lys Asn Lys
            340                 345                 350
Pro Leu Gly Pro Ala Gly Ser Glu Asn Glu Ile Pro Thr His Val Leu
        355                 360                 365
Pro Pro Cys Ala Asn Leu Gln Ala Gln Lys Leu Lys Ser Asn Val Ser
    370                 375                 380
Gly Asn Thr His Leu Cys Ile Ser Asn Gly Asn Tyr Glu Lys Glu Gly
385                 390                 395                 400
Leu Gly Ala Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                405                 410                 415
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            420                 425                 430
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        435                 440                 445
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    450                 455                 460
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
465                 470                 475                 480
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                485                 490                 495
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            500                 505                 510
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        515                 520                 525
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    530                 535                 540
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
545                 550                 555                 560
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                565                 570                 575
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            580                 585                 590
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        595                 600                 605
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    610                 615                 620
Ser Leu Ser Leu Ser Pro Gly Lys
625                 630
```

<210> 377
<211> 405
<212> PRT
<213> Artificial Sequence

<220>
<223> Cynomolgus GFRalpha3: cerebellum cDNA

<400> 377

```
Met Val Arg Pro Pro Ser Pro Arg Pro Leu Pro Pro Val Val Leu Met
 1               5                  10                  15
Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Pro Pro Ser Pro Leu Pro
            20                  25                  30
Leu Ala Ala Gly Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser
        35                  40                  45
Cys Leu Gln Ala Arg Arg Lys Cys Gln Ala Asp Pro Ile Cys Ser Ala
    50                  55                  60
Ala Tyr His His Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu
65                  70                  75                  80
Pro Ser Glu Glu Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln
                85                  90                  95
Gln Leu Arg Asn Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met
            100                 105                 110
Lys Asn Gln Val Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala
        115                 120                 125
Arg Ser Leu Gly Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr
    130                 135                 140
Val Thr Ser Lys Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu
145                 150                 155                 160
Lys Pro Asp Ser Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu
                165                 170                 175
Asn Asp Lys Cys Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser
            180                 185                 190
Gly Pro His Cys Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe
        195                 200                 205
Phe Glu Lys Ala Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro
    210                 215                 220
Cys Ala Pro Asn Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile
225                 230                 235                 240
Ala Pro Ser Cys Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu
                245                 250                 255
Arg Arg Leu Cys Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp
            260                 265                 270
Phe Gln Thr His Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr
        275                 280                 285
Glu Gln Ser Arg Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala
    290                 295                 300
Met Thr Pro Asn Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser
305                 310                 315                 320
Cys Thr Cys Arg Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Gln Leu
                325                 330                 335
Glu Gly Phe Phe Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala
            340                 345                 350
Lys Met Arg Phe His Ser Gln Leu Phe Tyr Gln Asp Trp Pro His Pro
        355                 360                 365
Thr Phe Ala Val Met Ala His Gln Asn Glu Asn Arg Ala Leu Arg Ser
    370                 375                 380
Lys Pro Trp Ala Pro Ser Leu Phe Ser Cys Thr Leu Pro Leu Ile Leu
385                 390                 395                 400
Leu Leu Ser Leu Trp
                405
```

<210> 378
<211> 1086
<212> PRT
<213> Artificial Sequence

<220>
<223> Cynomolgus RET without signal sequence

<400> 378

```
Leu Tyr Phe Ser Arg Asp Ala Tyr Trp Glu Lys Leu Tyr Val Asp Gln
 1               5                  10                  15
Pro Ala Gly Thr Pro Leu Leu Tyr Val His Ala Leu Arg Asp Ala Pro
            20                  25                  30
Glu Glu Val Pro Ser Phe Arg Leu Gly Gln His Leu Tyr Gly Thr Tyr
        35                  40                  45
Arg Thr Arg Leu His Glu Asn Asn Trp Ile Cys Ile Gln Glu Asp Thr
    50                  55                  60
Gly Leu Leu Tyr Leu Asn Arg Ser Leu Asp Arg Ser Ser Trp Glu Lys
65                  70                  75                  80
Leu Ser Gly Arg Asn Arg Gly Phe Pro Leu Leu Thr Val Tyr Leu Lys
                85                  90                  95
Val Phe Leu Ser Pro Thr Ser Leu Arg Glu Gly Glu Cys Gln Trp Pro
            100                 105                 110
Gly Cys Ala Arg Val Tyr Phe Ser Phe Phe Asn Thr Ser Phe Pro Ala
        115                 120                 125
Cys Thr Ser Leu Lys Pro Arg Glu Leu Cys Phe Pro Glu Thr Arg Pro
    130                 135                 140
Ser Phe Arg Ile Arg Glu Asn Arg Pro Pro Gly Thr Phe His Gln Phe
145                 150                 155                 160
Arg Leu Leu Pro Val Gln Phe Leu Cys Pro Asn Ile Ser Val Ala Tyr
                165                 170                 175
Arg Leu Leu Glu Gly Glu Gly Leu Pro Phe Arg Cys Ala Pro Asp Ser
            180                 185                 190
Leu Glu Val Ser Thr Arg Trp Ala Leu Asp Arg Glu Gln Arg Glu Lys
        195                 200                 205
Tyr Glu Leu Val Ala Val Cys Thr Val His Ala Gly Ala Arg Glu Glu
    210                 215                 220
Val Val Met Val Pro Phe Pro Val Thr Val Tyr Asp Glu Asp Asp Ser
225                 230                 235                 240
Ala Pro Thr Phe Pro Ala Gly Val Asp Thr Ala Ser Ala Val Val Glu
                245                 250                 255
Phe Lys Arg Lys Glu Asp Thr Val Val Ala Thr Leu Arg Val Phe Asp
            260                 265                 270
Ala Asp Val Val Pro Ala Ser Gly Glu Leu Val Arg Arg Tyr Thr Ser
        275                 280                 285
Thr Leu Leu Pro Gly Asp Thr Trp Thr Gln Gln Thr Phe Arg Val Glu
    290                 295                 300
His Trp Pro Asn Glu Thr Ser Val Gln Ala Asn Gly Ser Phe Val Arg
305                 310                 315                 320
Ala Thr Val His Asp Tyr Arg Leu Val Leu Asn Arg Asn Leu Ser Ile
                325                 330                 335
Ser Glu Asn Arg Thr Met Gln Leu Ala Val Leu Val Asn Asp Ser Asp
            340                 345                 350
Phe Gln Gly Pro Gly Ala Gly Val Leu Leu Leu His Phe Asn Val Ser
        355                 360                 365
Val Leu Pro Val Ser Leu His Leu Pro Ser Ser Tyr Ser Leu Ser Val
    370                 375                 380
Ser Arg Arg Ala Arg Arg Phe Ala Gln Ile Gly Lys Val Cys Val Glu
385                 390                 395                 400
Asn Cys Gln Ala Phe Ser Gly Ile Asn Val Gln Tyr Glu Leu His Ser
                405                 410                 415
Ser Gly Ala Asn Cys Ser Thr Leu Gly Val Val Thr Ser Ala Glu Asp
            420                 425                 430
Thr Ser Gly Ile Leu Phe Val Asn Asp Thr Lys Ala Leu Arg Arg Pro
        435                 440                 445
Lys Cys Ala Glu Leu His Tyr Met Val Val Ala Thr Asn His Gln Thr
    450                 455                 460
```

```
Ser Arg Gln Ala Gln Ala Gln Leu Leu Val Thr Val Glu Gly Leu Tyr
465                 470                 475                 480
Val Ala Glu Glu Ala Gly Cys Pro Leu Ser Cys Ala Val Ser Lys Arg
                485                 490                 495
Arg Pro Glu Cys Glu Glu Cys Gly Gly Leu Gly Ser Pro Thr Gly Arg
            500                 505                 510
Cys Glu Trp Arg Gln Gly Asp Gly Lys Gly Ile Thr Arg Asn Phe Ser
        515                 520                 525
Thr Cys Ser Pro Ser Thr Lys Thr Cys Pro Asp Gly His Cys Asp Val
    530                 535                 540
Val Glu Thr Gln Asp Ile Asn Ile Cys Pro Gln Asp Cys Leu Arg Gly
545                 550                 555                 560
Ser Ile Val Gly Gly His Glu Pro Gly Glu Pro Arg Gly Ile Lys Ala
                565                 570                 575
Gly Tyr Gly Thr Cys Asn Cys Phe Pro Glu Glu Glu Lys Cys Phe Cys
            580                 585                 590
Glu Pro Glu Asp Ile Gln Asp Pro Leu Cys Asp Glu Leu Cys Arg Thr
        595                 600                 605
Val Ile Ala Ala Ala Val Leu Phe Ser Phe Ile Val Ser Val Leu Leu
    610                 615                 620
Ser Ala Phe Cys Ile His Arg Tyr His Lys Phe Ala His Lys Pro Pro
625                 630                 635                 640
Ile Pro Ser Ala Glu Met Thr Phe Arg Arg Pro Ala Gln Ala Phe Pro
                645                 650                 655
Val Ser Tyr Ser Ser Ser Gly Ala Arg Arg Pro Ser Leu Asp Ser Met
            660                 665                 670
Glu Asn Gln Val Ser Val Asp Ala Phe Lys Ile Pro Glu Asp Pro Lys
        675                 680                 685
Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr Leu Gly Glu
    690                 695                 700
Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe Arg Leu Lys Gly
705                 710                 715                 720
Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys Glu Asn Ala
                725                 730                 735
Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn Leu Leu Lys
            740                 745                 750
Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala Cys Ser Gln
        755                 760                 765
Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly Ser Leu
    770                 775                 780
Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr Leu Gly
785                 790                 795                 800
Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro Asp Glu Arg
                805                 810                 815
Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile Ser Arg
            820                 825                 830
Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg Asp Leu Ala
        835                 840                 845
Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys Met Lys Ile Ser Asp
    850                 855                 860
Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val Lys Arg
865                 870                 875                 880
Ser Lys Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu Ser Leu Phe
                885                 890                 895
Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe Gly Val Leu
            900                 905                 910
Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr Pro Gly Ile Pro
        915                 920                 925
Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly His Arg Met Glu Arg
    930                 935                 940
Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg Leu Met Leu Gln Cys Trp
945                 950                 955                 960
Lys Gln Glu Pro Asp Lys Arg Pro Val Phe Ala Asp Ile Ser Lys Asp
```

```
                965                 970                 975
Leu Glu Lys Met Met Val Lys Ser Arg Asp Tyr Leu Asp Leu Ala Ala
            980                 985                 990
Ser Thr Pro Ser Asp Ser Leu Leu Tyr Asp Asp Gly Leu Ser Glu Glu
        995                 1000                1005
Glu Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu
    1010                1015                1020
Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Met Ser Asp Pro Asn
1025                1030                1035                1040
Trp Pro Gly Glu Ser Pro Val Pro Leu Thr Arg Ala Asp Gly Thr Asn
                1045                1050                1055
Thr Gly Phe Pro Arg Tyr Ala Asn Asp Ser Val Tyr Ala Asn Trp Met
            1060                1065                1070
Leu Ser Pro Ser Ala Ala Lys Leu Met Asp Thr Phe Asp Ser
        1075                1080                1085
```

<210> 379
<211> 371
<212> PRT
<213> Artificial Sequence

<220>
<223> Mouse GFRalpha3-MMH
aa 1-343: N29-N371 of Ac. No. AAH66202.1
aa 344-371: myc-GG linker-myc-hexahistidine tag

<400> 379

```
Asn Ser Leu Ala Thr Glu Asn Arg Phe Val Asn Ser Cys Thr Gln Ala
 1               5                  10                  15
Arg Lys Lys Cys Glu Ala Asn Pro Ala Cys Lys Ala Ala Tyr Gln His
            20                  25                  30
Leu Gly Ser Cys Thr Ser Ser Leu Ser Arg Pro Leu Pro Leu Glu Glu
        35                  40                  45
Ser Ala Met Ser Ala Asp Cys Leu Glu Ala Ala Glu Gln Leu Arg Asn
    50                  55                  60
Ser Ser Leu Ile Asp Cys Arg Cys His Arg Arg Met Lys His Gln Ala
65                  70                  75                  80
Thr Cys Leu Asp Ile Tyr Trp Thr Val His Pro Ala Arg Ser Leu Gly
                85                  90                  95
Asp Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
            100                 105                 110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
        115                 120                 125
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu His Asp Lys Cys
    130                 135                 140
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Ile Arg Cys
145                 150                 155                 160
Gln Arg His Leu Cys Leu Ala Gln Leu Arg Ser Phe Phe Glu Lys Ala
                165                 170                 175
Ala Glu Ser His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Glu
            180                 185                 190
Asp Ala Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Ser Cys
        195                 200                 205
Ala Leu Pro Ser Val Thr Pro Asn Cys Leu Asp Leu Arg Ser Phe Cys
    210                 215                 220
Arg Ala Asp Pro Leu Cys Arg Ser Arg Leu Met Asp Phe Gln Thr His
225                 230                 235                 240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
                245                 250                 255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
            260                 265                 270
Phe Ile Ser Lys Val Asn Thr Thr Val Ala Leu Ser Cys Ser Cys Arg
```

```
        275                 280                 285
Gly Ser Gly Asn Leu Gln Asp Glu Cys Glu Gln Leu Glu Arg Ser Phe
    290                 295                 300
Ser Gln Asn Pro Cys Leu Val Glu Ala Ile Ala Ala Lys Met Arg Phe
305                 310                 315                 320
His Arg Gln Leu Phe Ser Gln Asp Trp Ala Asp Ser Thr Phe Ser Val
                325                 330                 335
Val Gln Gln Gln Asn Ser Asn Glu Gln Lys Leu Ile Ser Glu Glu Asp
            340                 345                 350
Leu Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu His His His
        355                 360                 365
His His His
    370
```

<210> 380
<211> 372
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 380
caggttcaac tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggtta cacctttacc agctatggta tcatctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaatggtaa cacaaactat 180
acacagaatc tccagggcag agtcaccatg accacagaca cttccacgac cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagatggggt 300
atagcaactc gtccctacta ctactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

<210> 381
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 381
```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Gly Ile Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Trp Ile Ser Gly Tyr Asn Gly Asn Thr Asn Tyr Thr Gln Asn Leu
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Thr Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Gly Ile Ala Thr Arg Pro Tyr Tyr Tyr Tyr Gly Met Asp
            100                 105                 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 382
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 382
ggttacacct ttaccagcta tggt 24

<210> 383
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 383
Gly Tyr Thr Phe Thr Ser Tyr Gly
1 5

<210> 384
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 384
atcagcggtt acaatggtaa caca 24

<210> 385
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 385
Ile Ser Gly Tyr Asn Gly Asn Thr
1 5

<210> 386
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 386
gcgagatggg gtatagcaac tcgtccctac tactactacg gtatggacgt c 51

<210> 387
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 387
Ala Arg Trp Gly Ile Ala Thr Arg Pro Tyr Tyr Tyr Tyr Gly Met Asp
1 5 10 15
Val

<210> 388
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 388
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggacattacc aattatttag cctggtttca gcagaaacca 120
gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacag tataatagtt accctcccac tttcggccct 300
gggaccaaag tggatatcaa a 321

<210> 389
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 389
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Thr Asn Tyr
20 25 30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
85 90 95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 390
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 390
caggacatta ccaattat 18

<210> 391
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 391
Gln Asp Ile Thr Asn Tyr
1 5

<210> 392
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 392
gctgcatcc 9

<210> 393
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 393
Ala Ala Ser
1

<210> 394
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic

<400> 394
caacagtata atagttaccc tcccact 27

<210> 395
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 395
Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 396
<211> 369
<212> DNA
<213> Artificial Sequence

<220>

<223> synthetic

<400> 396
gaggtgcagt tattggagtc tgggggaac ttggtacagc cgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agttatgcca tgacctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaact attagtggta gtggtaccag cacatattac 180
gcagactccg tgaagggccg gttcaccatc tccagggaca attccaggga cacggtgttt 240
ctacaaatga acagcctgag agccgaggac acggccgtat attactgttc gaaaccttct 300
gcattacgat ttttacattg gttatgtatg gacgtctggg gccaagggac cctggtcacc 360
gtctcctca 369

<210> 397
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 397
Glu Val Gln Leu Leu Glu Ser Gly Gly Asn Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Thr Ile Ser Gly Ser Gly Thr Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asp Thr Val Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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gggaaagccc ctaagtccct gatctatgct gcatccaatt tgcaaagtgg ggtcccatca 180
aggttcggcg gcagtggatc tgggacagat ttcactctca ccatcaacag cctgcagcct 240
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20 25 30
Leu Asp Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45
Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Gly Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Val Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
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Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
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<400> 411
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1 5

Claims

1. An anti-GFRα3 antibody or antigen-binding fragment thereof comprising an HCVR/LCVR pair encoded by a nucleic acid sequence pair selected from the group consisting of:

(i) SEQ ID NO: 1 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 9 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(ii) SEQ ID NO: 17 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 25 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(iii) SEQ ID NO: 33 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 41 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(iv) SEQ ID NO: 49 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 57 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(v) SEQ ID NO: 65 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 73 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(vi) SEQ ID NO: 81 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 89 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(vii) SEQ ID NO: 97 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 105 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;

(viii) SEQ ID NO: 113 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 121 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(ix) SEQ ID NO: 129 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 137 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(x) SEQ ID NO: 145 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 153 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xi) SEQ ID NO: 161 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 169 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xii) SEQ ID NO: 177 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 185 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xiii) SEQ ID NO: 193 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 201 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xiv) SEQ ID NO: 209 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 217 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xv) SEQ ID NO: 225 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 233 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xvi) SEQ ID NO: 241 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 249 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xvii) SEQ ID NO: 257 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 265 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xviii) SEQ ID NO: 273 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 281 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xix) SEQ ID NO: 289 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 297 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xx) SEQ ID NO: 305 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 313 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xxi) SEQ ID NO: 321 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 329 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xxii) SEQ ID NO: 337 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 345 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xxiii) SEQ ID NO: 353 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 361 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(xxiv) SEQ ID NO: 380 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 388 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto; and
(xxv) SEQ ID NO: 396 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 404 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto.

2. The antibody or an antigen-binding fragment thereof of claim 1, having one or more of the following characteristics:

(i) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance;

(ii) demonstrates the ability to block about 50-100% of the binding of GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM;
(iii) demonstrates the ability to block about 20% to about 100% of the binding of GFRα3 to a solid support coated with a mixture of artemin and RET;
(iv) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM;
(v) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain;
(vi) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo;*
(vii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis; or
(viii) does not cross-react with other GFR co-receptors for RET.

3. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, wherein:

(a) the antibody is selected from the group consisting of a chimeric antibody, a humanized antibody and a human antibody, and/or;
(b) wherein the antibody does not cross-react with human GFRα1 or human GFRα2.

4. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, wherein:

(a) the antibody demonstrates the ability to block about 50-95% of the binding of human GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 750 pM;
(b) the antibody or the antigen-binding fragment thereof blocks about 75-100% of the binding of human GFRα3 to its ligand, artemin, with an IC_{50} value ranging from about 400 pM to about 15 nM;
(c) the antibody or the antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of human RET with an IC_{50} ranging from about 300 pM to about 5 nM; or
(d) the antibody or the antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of cynomolgus RET with an IC_{50} ranging from about 0.7 nM to about 2.5 nM.

5. The antibody or antigen-binding fragment thereof of any one of the preceding claims, comprising an HCVR/LCVR pair encoded by a nucleic acid sequence pair selected from the group consisting of:

(i) SEQ ID NO: 49 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 57 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(ii) SEQ ID NO: 145 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 153 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto;
(iii) SEQ ID NO: 209 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 217 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto; and
(iv) SEQ ID NO: 289 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, and SEQ ID NO: 297 or a sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity thereto.

6. An isolated nucleic acid molecule encoding the antibody or antigen-binding fragment of any of claims 1-5.

7. An expression vector comprising the nucleic acid molecule of claim 6.

8. A method of producing an anti-GFRα3 antibody or antigen-binding fragment thereof comprising the steps of introducing the expression vector of claim 7 into an isolated host cell, growing the cell under conditions permitting production of the antibody or fragment thereof, and recovering the antibody so produced.

9. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any one of claims 1-5 and a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition comprising an antibody or antigen-binding fragment thereof according to any one of claims 1-5 and a second therapeutic agent selected from the group consisting of an opioid, a COX-2 inhibitor, a local anesthetic, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a second GFRα3 antagonist, a cytokine or cytokine receptor antagonist, a nerve growth factor (NGF) inhibitor (a small molecular inhibitor or an anti-NGF antibody), an inhibitor of BDNF, TrkA, TrkB or p75,

aspirin, a NSAID, a steroid, morphine, a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a tricyclic, an inhibitor of a voltage-gated sodium channel (Na_v), a calcium channel inhibitor, a potassium channel inhibitor, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of GFRα1, GFRα2 or GFRα4, an inhibitor of an acid sensing ion channel (ASIC1 or ASIC3), an anti-convulsant (gabapentin or pregabalin), an inhibitor of a prokineticin receptor (PROK1 and PROK2), a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig and a corticosteroid; and a pharmaceutically acceptable carrier or diluent;
optionally wherein the second GFRα3 antagonist is a small organic molecule, a polypeptide antagonist, a second antibody specific for GFRα3, a siRNA or an antisense molecule specific for GFRα3; or wherein the cytokine or cytokine receptor antagonist is an interleukin-1 (IL-1) antagonist, an IL-6 antagonist, or an IL-18 antagonist.

11. The isolated antibody or antigen-binding fragment thereof according to any one of claims 1-5, or the pharmaceutical composition of either claim 9 or 10, for use in treating the pain associated with thermal hyperalgesia, wherein the pain associated with thermal hyperalgesia is prevented, ameliorated, or reduced in severity or frequency of occurrence.

12. The antibody or antigen-binding fragment thereof according to any one of claims 1-5, or the pharmaceutical composition of either claim 9 or 10, for use in treating pain associated with bone cancer, wherein the pain associated with bone cancer is prevented, ameliorated, or reduced in severity or frequency of occurrence.

13. The antibody, antigen-binding fragment, or pharmaceutical composition for use according to claim 11 or 12, wherein said antibody, antigen-binding fragment or pharmaceutical composition is for administration to a patient in combination with a second therapeutic agent; wherein said second therapeutic agent is optionally as defined in claim 10.

14. The antibody or antigen-binding fragment thereof of claim 1, comprising an HCDR1 amino acid sequence of SEQ ID NO: 148; an HCDR2 amino acid sequence of SEQ ID NO: 150; an HCDR3 amino acid sequence of SEQ ID NO: 152; an LCDR1 amino acid sequence of SEQ ID NO: 156; an LCDR2 amino acid sequence of SEQ ID NO: 158; and an LCDR3 amino acid sequence of SEQ ID NO: 160.

15. The antibody or antigen-binding fragment thereof of claim 1, comprising an HCVR amino acid sequence of SEQ ID NO: 146 or the CDRs contained therein, and/or an LCVR amino acid sequence of SEQ ID NO: 154 or the CDRs contained therein.

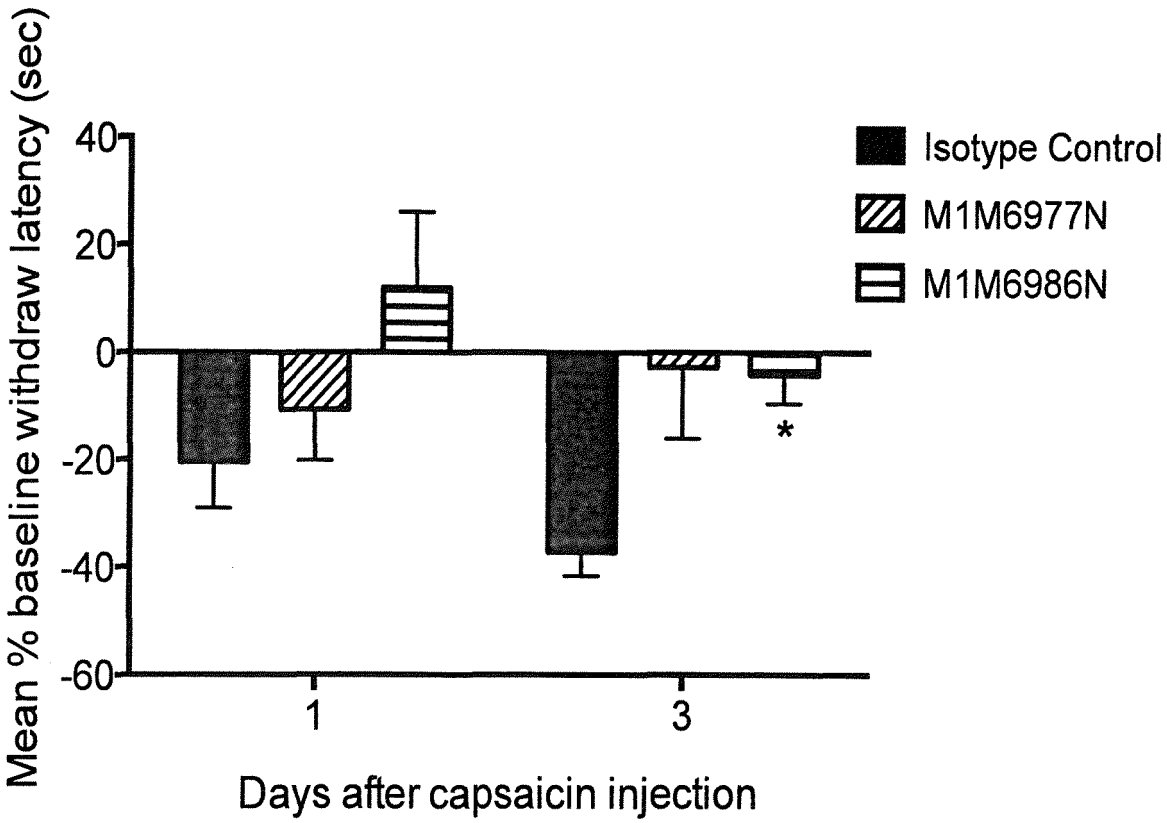
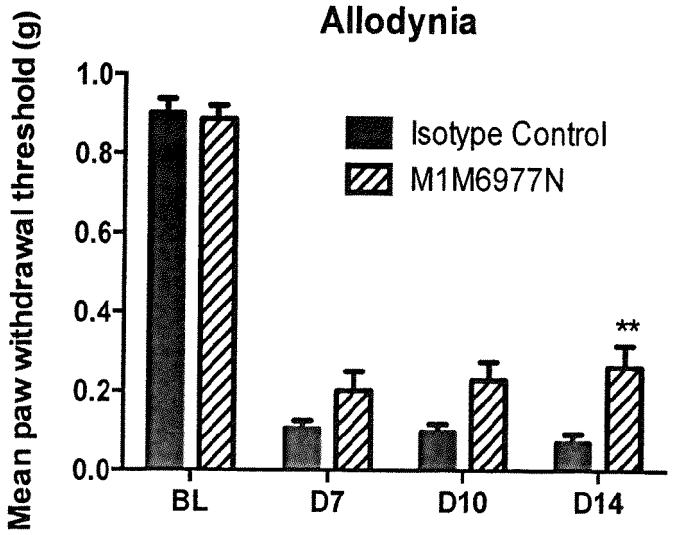

Mean % baseline withdraw latency (sec)
40
20
0
-20
-40
-60
1
3
*
Days after capsaicin injection
Isotype Control
M1M6977N
M1M6986N

Figure 1

A.


Allodynia
Mean paw withdrawal threshold (g)
1.0
0.8
0.6
0.4
0.2
0.0
Isotype Control
M1M6977N
**
BL
D7
D10
D14

B.

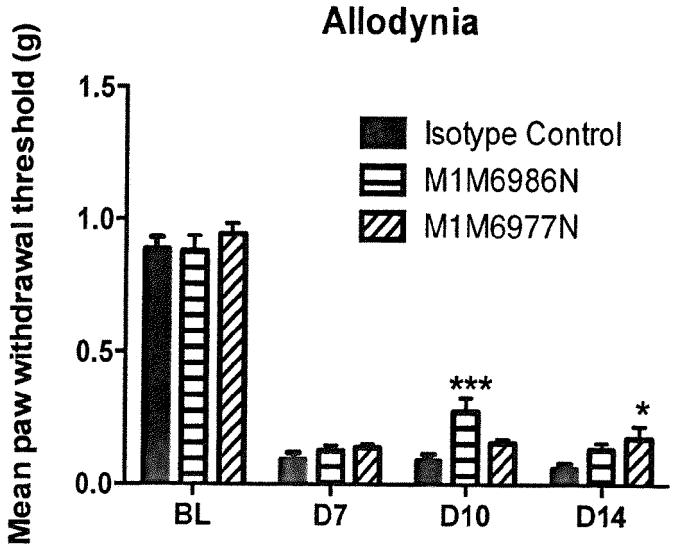
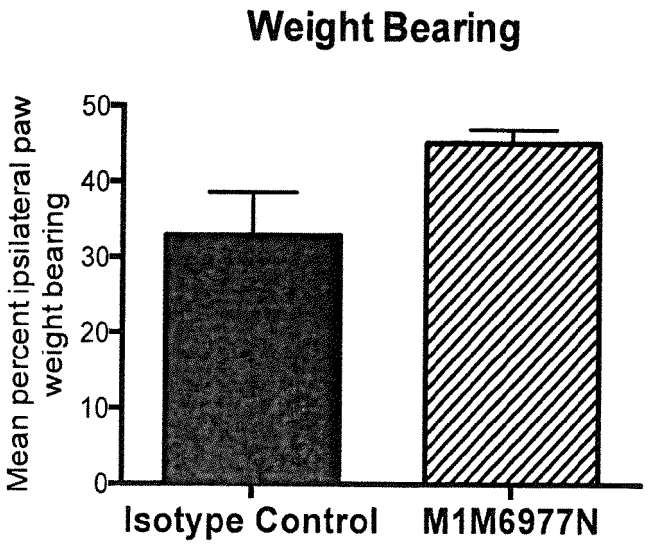

Allodynia
Mean paw withdrawal threshold (g)
1.5
1.0
0.5
0.0
Isotype Control
M1M6986N
M1M6977N
***
*
BL
D7
D10
D14

Figure 2

A.


Weight Bearing
Mean percent ipsilateral paw weight bearing
50
40
30
20
10
0
Isotype Control
M1M6977N

B.

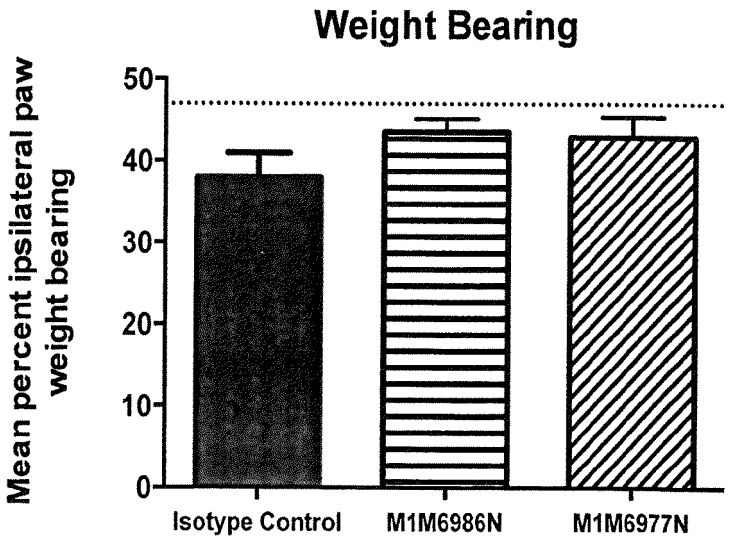
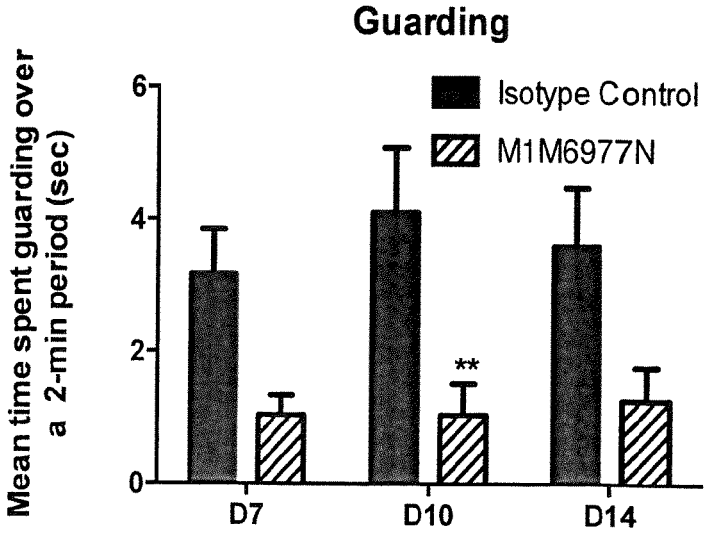

Weight Bearing
Mean percent ipsilateral paw weight bearing
50
40
30
20
10
0
Isotype Control
M1M6986N
M1M6977N

Figure 3

A.


Guarding
Mean time spent guarding over a 2-min period (sec)
6
4
2
0
Isotype Control
M1M6977N
**
D7
D10
D14

B.

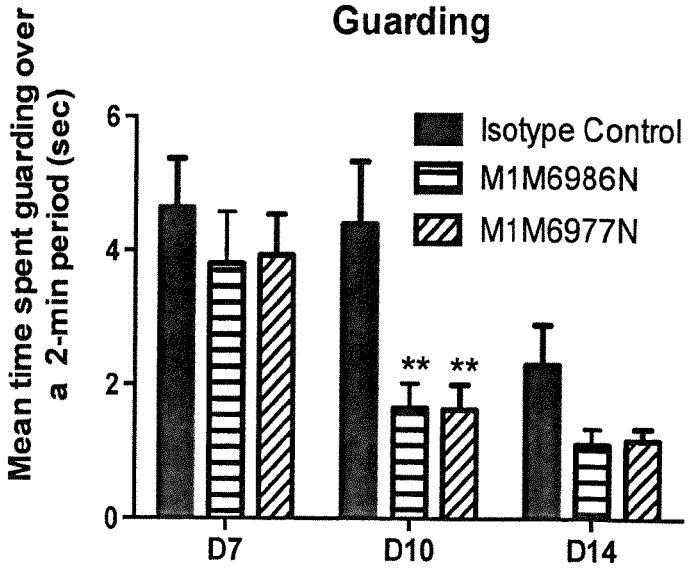

Guarding
Mean time spent guarding over a 2-min period (sec)
6
4
2
0
Isotype Control
M1M6986N
M1M6977N
** **
D7
D10
D14

Figure 4

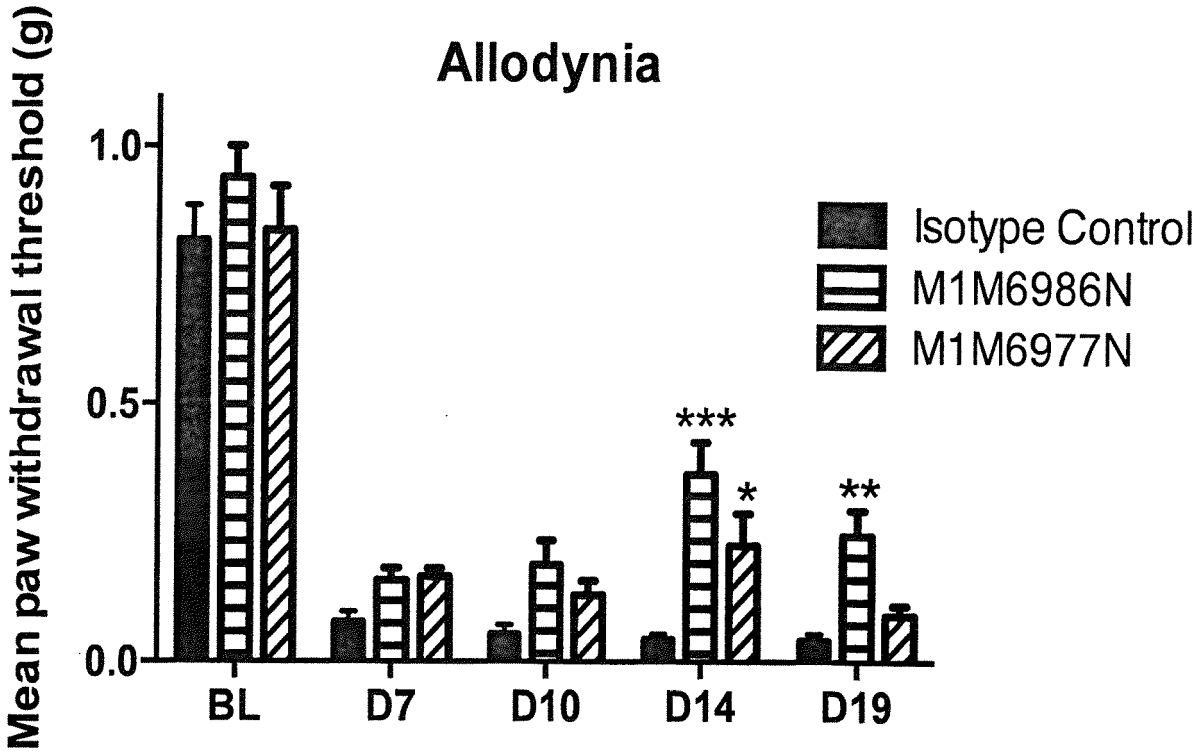
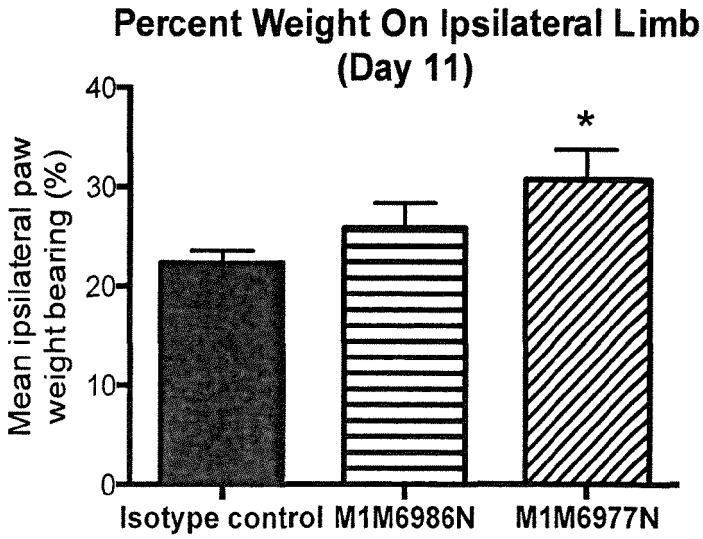

Allodynia
Mean paw withdrawal threshold (g)
1.0
0.5
0.0
BL
D7
D10
D14
D19
***
*
**
Isotype Control
M1M6986N
M1M6977N

Figure 5

A.


Percent Weight On Ipsilateral Limb
(Day 11)
Mean ipsilateral paw weight bearing (%)
40
30
20
10
0
*
Isotype control
M1M6986N
M1M6977N

B.

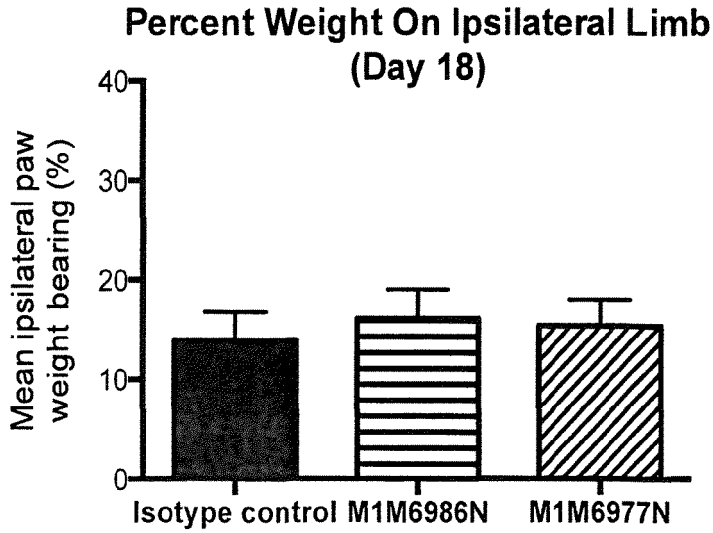

Percent Weight On Ipsilateral Limb
(Day 18)
Mean ipsilateral paw weight bearing (%)
40
30
20
10
0
Isotype control
M1M6986N
M1M6977N

Figure 6

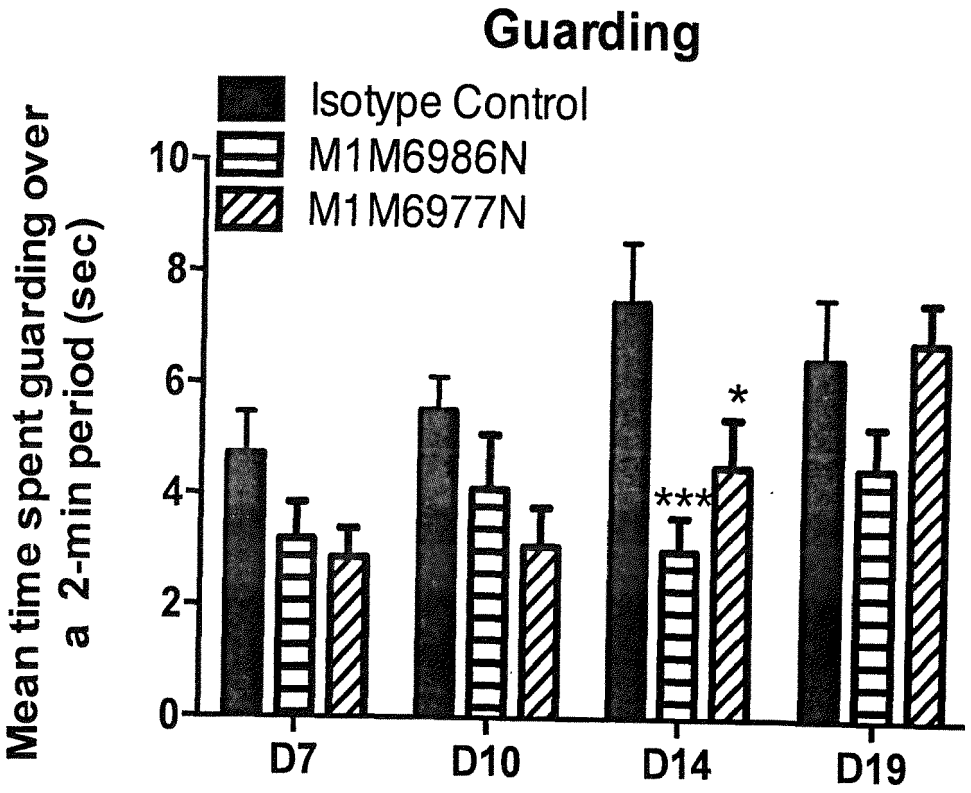

Guarding
Isotype Control
M1M6986N
M1M6977N
Mean time spent guarding over a 2-min period (sec)
10
8
6
4
2
0
***
*
D7
D10
D14
D19

Figure 7

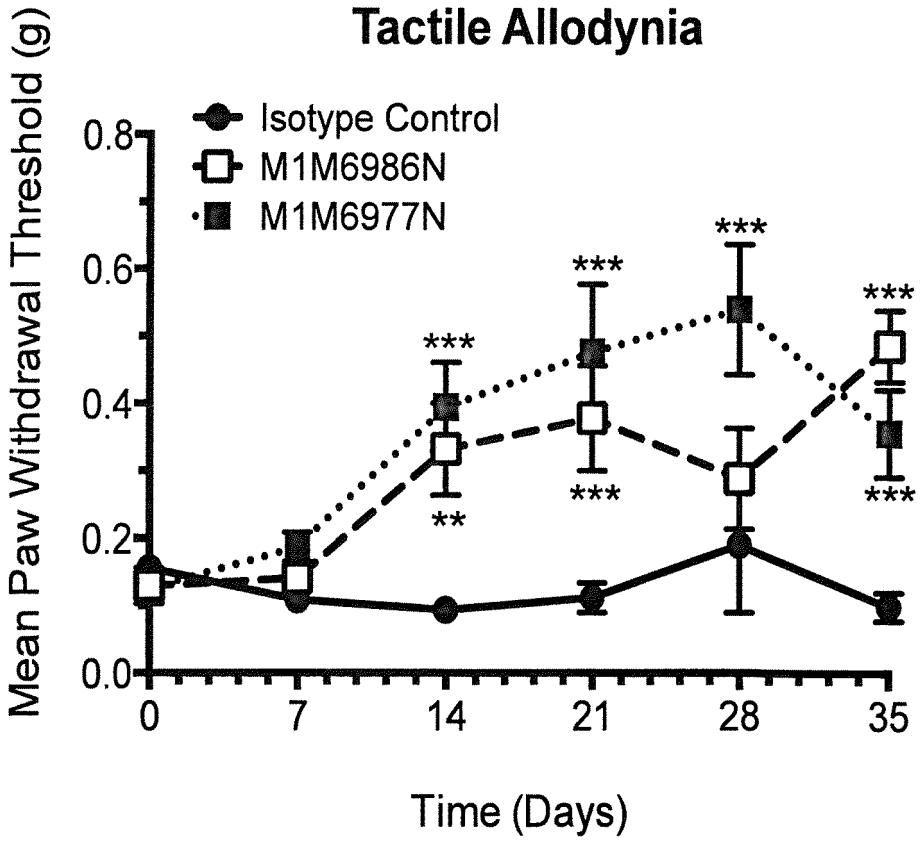

Tactile Allodynia
Isotype Control
M1M6986N
M1M6977N
Mean Paw Withdrawal Threshold (g)
0.0
0.2
0.4
0.6
0.8
0
7
14
21
28
35
Time (Days)
**
***
***
***
***
***

Figure 8

Figure 9

Antibody	Biotin-human GFRα3 captured (nm)	Amount of Antibody 1 bound (nm)	H4H2236N3	H4H2342P	H4H2295S	H4H2294S	H4H2291S	H4H2357S	H4H2355S	H4H2296S	H4H2243N2	H4H2212N	H4H2352S	H4H2292S	H4H2350P
H4H2236N3	1.07 ± 0.08	2.64 ± 0.18	0.00	-0.01	0.03	0.00	0.06	0.04	0.00	0.02	0.02	1.79	1.91	1.81	1.35
H4H2342P	1.09 ± 0.08	2.69 ± 0.17	0.20	0.06	0.31	0.23	0.45	0.25	0.16	0.28	0.11	1.76	1.72	1.85	1.46
H4H2295S	1.14 ± 0.15	2.83 ± 0.27	0.01	0.01	0.05	0.02	0.20	0.05	0.02	0.07	0.01	1.81	1.85	1.80	1.35
H4H2294S	1.22 ± 0.04	2.91 ± 0.09	0.05	0.01	0.04	0.02	0.12	0.03	0.00	0.04	0.03	1.92	1.99	1.92	1.42
H4H2291S	1.16 ± 0.04	2.89 ± 0.08	0.01	-0.01	0.00	0.00	0.05	0.00	0.00	-0.01	0.00	1.96	2.03	1.94	1.44
H4H2357S	1.15 ± 0.03	2.82 ± 0.07	0.04	-0.01	0.12	0.05	0.18	0.04	0.00	0.06	0.01	1.90	2.00	1.92	1.35
H4H2355S	1.15 ± 0.03	2.73 ± 0.07	0.18	0.06	0.20	0.16	0.31	0.16	0.07	0.18	0.09	1.95	1.97	1.92	1.44
H4H2296S	1.29 ± 0.13	2.88 ± 0.23	0.07	0.03	0.05	0.04	0.18	0.06	0.02	0.07	0.06	1.76	2.01	1.87	1.27
H4H2243N2	1.10 ± 0.08	2.42 ± 0.17	0.30	0.15	0.39	0.29	0.52	0.32	0.24	0.33	0.06	0.22	0.46	1.70	1.20
H4H2212N	1.09 ± 0.08	2.32 ± 0.15	2.14	2.17	2.15	2.12	2.69	2.38	2.05	2.36	0.16	0.05	0.08	1.76	1.36
H4H2352S	1.15 ± 0.03	2.74 ± 0.16	2.15	2.08	2.31	2.25	2.63	2.45	2.12	2.35	0.13	0.05	0.10	0.15	1.43
H4H2292S	1.17 ± 0.04	2.82 ± 0.08	2.24	2.16	2.31	2.31	2.81	2.43	2.07	2.36	1.91	1.78	0.34	0.11	1.53
H4H2350P	1.09 ± 0.07	3.31 ± 0.15	1.98	1.80	2.05	2.00	2.57	2.23	1.77	2.10	1.72	1.57	2.06	1.74	0.25

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EUROPEAN SEARCH REPORT

Application Number
EP 18 20 0535

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 2006/138721 A1 (BIOGEN IDEC INC [US]; WORLEY DANE S [US]; SAH DINAH WEN-YEE [US]; SEAM) 28 December 2006 (2006-12-28) * page 30, line 1 - line 2; claims 1-35; figure 7; examples 1-5 *	1-15	INV. C07K16/28 A61P29/00 A61K39/395
X	US 7 026 138 B1 (DE SAUVAGE FREDERIC J [US] ET AL) 11 April 2006 (2006-04-11) * example 11 *	1-15	
X	R&D SYSTEMS ET AL: "Anti-mouse GFRalpha3 antibody", INTERNET CITATION , no. 1-800-343-7475 page 1, XP002531393, Retrieved from the Internet: URL:http://www.rndsystems.com/pdf/AF2645.pdf [retrieved on 2009-06-09] * the whole document *	1-15	

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	19 November 2018	Siaterli, Maria

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